



Europäisches
Patentamt

European
Patent Office

Office européen
des brevets

REC'D 13 JAN 2005

WIPO

PCT

Bescheinigung

Certificate

Attestation

Die angehefteten Unterla-
gen stimmen mit der
ursprünglich eingereichten
Fassung der auf dem näch-
sten Blatt bezeichneten
europäischen Patentanmel-
dung überein.

The attached documents
are exact copies of the
European patent application
described on the following
page, as originally filed.

Les documents fixés à
cette attestation sont
conformes à la version
initialement déposée de
la demande de brevet
européen spécifiée à la
page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

04380159.6

**PRIORITY
DOCUMENT**
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH RULE 17.1(a) OR (b)

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

BEST AVAILABLE COPY



Anmeldung Nr:
Application no.: 04380159.6
Demande no:

Anmeldetag:
Date of filing: 21.07.04
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

ELI LILLY AND COMPANY
Lilly Corporate Center
Indianapolis, Indiana 46285
ETATS-UNIS D'AMERIQUE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Triazole, oxadiazole and thiadiazole derivative PPAR modulators

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s)
revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07D249/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of
filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL
PL PT RO SE SI SK TR LI

The original title of the application in the Spanish language reads as follows : Moduladores
de PPAR derivados de triazol, oxadiazol y tiadiazol.

**TRIAZOLE, OXADIAZOLE AND THIADIAZOLE DERIVATIVE PPAR
MODULATORS**

BACKGROUND OF THE INVENTION

5

Peroxisome Proliferator Activated Receptors (PPARs) are members of the nuclear hormone receptor superfamily, a large and diverse group of proteins that mediate ligand-dependent transcriptional activation and repression. Three subtypes of PPARs have been isolated: PPAR α , PPAR γ and PPAR δ .

10

The expression profile of each isoform differs significantly from the others, whereby PPAR α is expressed primarily, but not exclusively in liver; PPAR γ is expressed primarily in adipose tissue; and PPAR δ is expressed ubiquitously. Studies of the individual PPAR isoforms and ligands have revealed their regulation of processes involved in insulin resistance and diabetes, as well as lipid disorders, such as

15 hyperlipidemia and dyslipidemia. PPAR γ agonists, such as pioglitazone, can be useful in the treatment of non-insulin dependent diabetes mellitus. Such PPAR γ agonists are associated with insulin sensitization.

20

PPAR α agonists, such as fenofibrate, can be useful in the treatment of hyperlipidemia. Although clinical evidence is not available to reveal the utility of PPAR δ agonists in humans, several preclinical studies suggest that PPAR δ agonists can be useful in the treatment of diabetes and lipid disorders.

25

The prevalence of the conditions that comprise Metabolic Syndrome (obesity, insulin resistance, hyperlipidemia, hypertension and atherosclerosis) continues to increase. New pharmaceutical agents are needed to address the unmet clinical needs of patients.

30

PPAR δ agonists have been suggested as a potential treatment for use in regulating many of the parameters associated with Metabolic Syndrome and Atherosclerosis. For example, in obese, non-diabetic rhesus monkeys, a PPAR δ agonist reduced circulating triglycerides and LDL, decreased basal insulin levels and increased HDL (Oliver, W.R. *et al.* Proc Natl Acad Sci 98:5306-5311; 2001). The insulin sensitization observed with the

use of a PPAR δ agonist is thought to be in part due to decreased myocellular lipids (Dressel, U. et al. Mol Endocrinol 17:2477-2493; 2003).

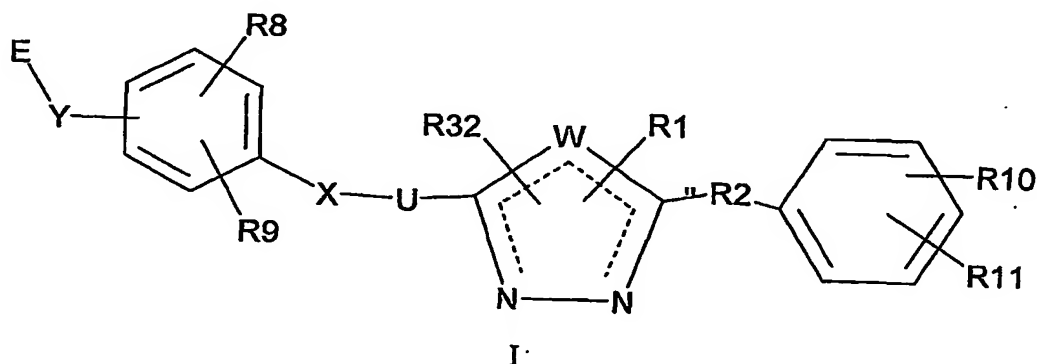
Further, atherosclerosis is considered to be a disease consequence of dyslipidemia and may be associated with inflammatory disease. C-reactive protein (CRP) production is part of the acute-phase response to most forms of inflammation, infection and tissue damage. It is measured diagnostically as a marker of low-grade inflammation. Plasma CRP levels of greater than 3 mg/L have been considered predictive of high risk for coronary artery disease (J. Clin. Invest 111: 1085-1812, 2003).

PPAR δ agonists are believed to mediate anti-inflammatory effects. Indeed, treatment of LPS-stimulated macrophages with a PPAR δ agonist has been observed to reduce the expression of iNOS, IL-12, and IL-6 (Welch, J.S. et al. Proc Natl Acad Sci 100:6712-6717 2003).

It may be especially desirable when the active pharmaceutical agent selectively modulates a PPAR receptor subtype to provide an especially desirable pharmacological profile. In some instances, it can be desirable when the active pharmacological agent selectively modulates more than one PPAR receptor subtype to provide a desired pharmacological profile.

SUMMARY OF THE INVENTION

The present invention is directed to compounds represented by the following structural Formula I:



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

- (a) R1 is selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ alkenyl, C₁-C₈ heteroalkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and, wherein C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents independently selected from R1';
- (b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR12, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₀₋₄-alkyl, heteroaryl, heterocycloalkyl, C(O)R13, COOR14, OC(O)R15, OS(O)₂R16, N(R17)₂, NR18C(O)R19, NR20SO₂R21, SR22, S(O)R23, S(O)₂R24, and S(O)₂N(R25)₂; R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24 and R25 are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (c) R2 is selected from the group consisting of C₀-C₈ alkyl and C₁₋₄-heteroalkyl;
- (d) X is selected from the group consisting of a single bond, O, S, S(O)₂ and N;
- (e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R30;
- (f) W is N, O or S;
- (g) Y is selected from the group consisting of C, NH, and a single bond;
- (h) E is C(R3)(R4)A or A and wherein
- (i) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkynitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each

optionally substituted with from one to two groups independently selected from R⁷;

(ii) each R⁷ is independently selected from the group consisting of hydrogen, C₁-C₆ haloalkyl, aryl C₀-C₄ alkyl and C₁-C₆ alkyl;

(iii) R₃ is selected from the group consisting of hydrogen, C₁-C₅ alkyl, and C₁-C₅ alkoxy; and

(iv) R₄ is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R₃ and R₄ are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R₂₆;

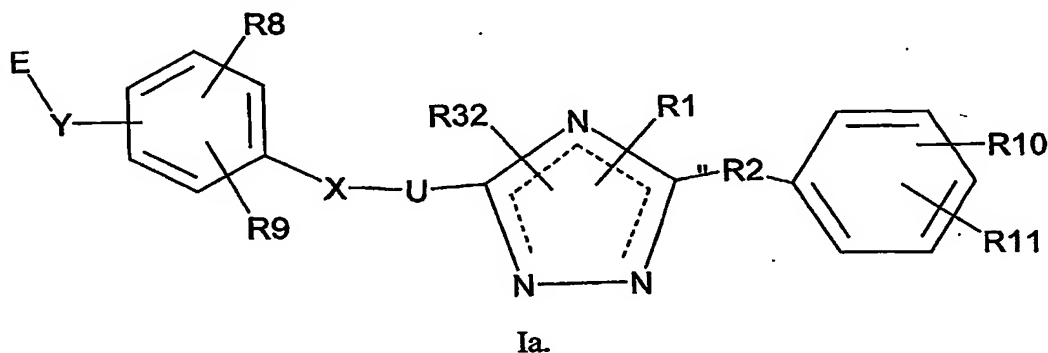
(i) R₈ is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, and halo;

(j) R₉ is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, halo, aryl-C₀-C₄ alkyl, heteroaryl, C₁-C₆ allyl, and OR₂₉, and wherein aryl-C₀-C₄ alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R₂₇; R₂₉ is selected from the group consisting of hydrogen and C₁-C₄ alkyl;

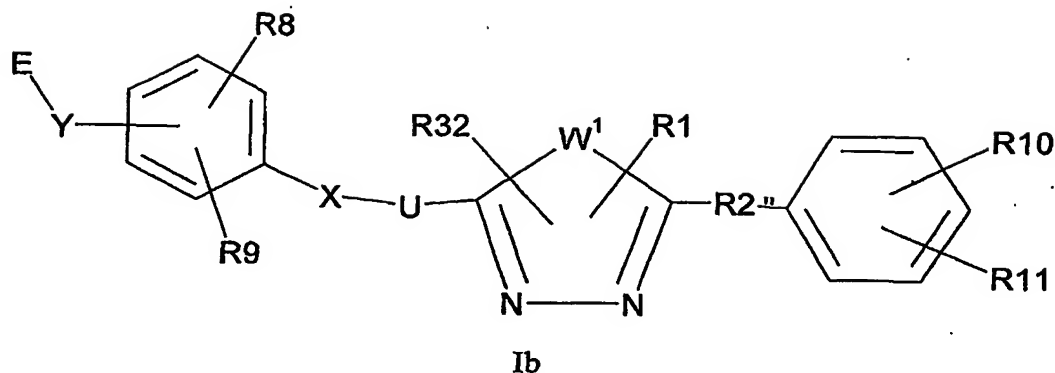
(k) R₁₀, R₁₁ are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkylenyl, C₁-C₆ alkyl-COOR₁₂'', C₀-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, aryloxy, C(O)R₁₃', COOR₁₄', OC(O)R₁₅', OS(O)₂R₁₆', N(R₁₇')₂, NR₁₈'C(O)R₁₉', NR₂₀'SO₂R₂₁', SR₂₂', S(O)R₂₃', S(O)₂R₂₄', and S(O)₂N(R₂₅')₂; and wherein aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three independently selected from

- R28; and wherein R10 and R11 optionally combine to form a 5 to 6 membered fused bicyclic ring with the phenyl to which they are bound;
- (l) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (m) R30 is selected from the group consisting of C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and wherein C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents each independently selected from R31;
- (n) R32 is selected from the group consisting of a hydrogen, halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, and C₁-C₆ alkyloxo; and
- (o) ---- is optionally a bond to form a double bond at the indicated position.

A further embodiment of the present invention is a compound of the Formula Ia:

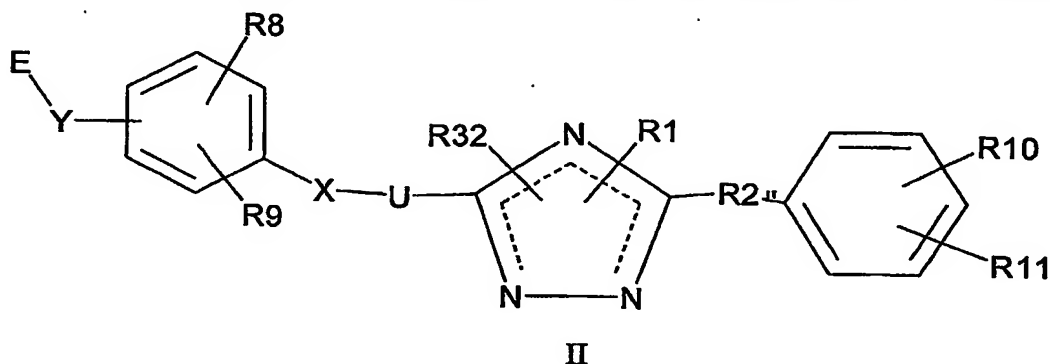


A further embodiment of the present invention is a compound of the Formula Ib



wherein W¹ is O or S.

5 A further embodiment of the present invention is a compound of the Formula II:



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof,
 10 wherein:

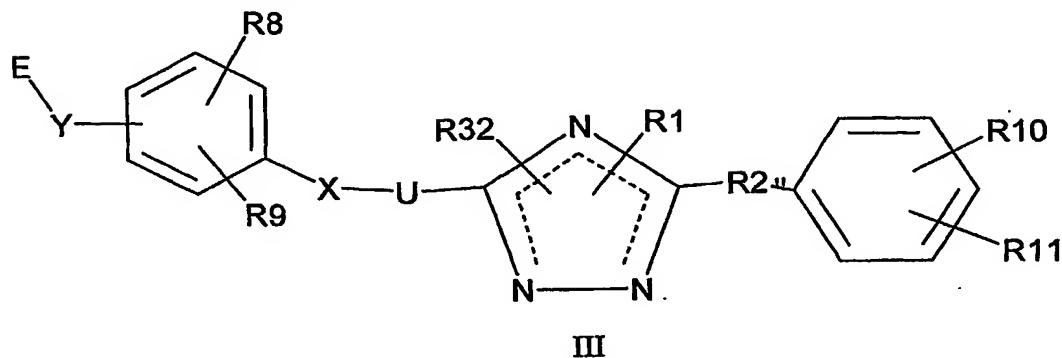
- (a) R₁ is selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and, wherein C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents independently selected from R₁';
- (b) R₁', R₂₆, R₂₇, R₂₈ and R₃₁ are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR₁₂, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆

haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₀₋₄-alkyl, heteroaryl, heterocycloalkyl, C(O)R₁₃, COOR₁₄, OC(O)R₁₅, OS(O)₂R₁₆, N(R₁₇)₂, NR₁₈C(O)R₁₉, NR₂₀SO₂R₂₁, SR₂₂, S(O)R₂₃, S(O)₂R₂₄, and S(O)₂N(R₂₅)₂; R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄ and R₂₅ are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;

- (c) R₂ is selected from the group consisting of C₀-C₈ alkyl and C₁₋₄-heteroalkyl;
- (d) X is selected from the group consisting of a single bond, O, S, S(O)₂ and N;
- (e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is substituted with from one to four substituents each independently selected from R₃₀;
- (f) Y is selected from the group consisting of C, O, S, NH and a single bond;
- (g) E is C(R₃)(R₄)A or A and wherein
- (i) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkynitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R⁷;
 - (ii) each R⁷ is independently selected from the group consisting of hydrogen, C₁-C₆ haloalkyl, aryl C₀-C₄ alkyl and C₁-C₆ alkyl;
 - (iii) R₃ is selected from the group consisting of hydrogen, C₁-C₅ alkyl, and C₁-C₅ alkoxy; and
 - (iv) R₄ is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R₃ and R₄ are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R₂₆;

- (h) R8 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, and halo;
- (i) R9 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, halo, aryl-C₀-C₄ alkyl, heteroaryl, C₁-C₆ allyl, and OR29, and wherein aryl-C₀-C₄ alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C₁-C₄ alkyl;
- (j) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkylenyl, C₁-C₆ alkyl-COOR12'', C₀-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', OS(O)₂R16', N(R17')₂, NR18'C(O)R19', NR20'SO₂R21', SR22', S(Ö)R23', S(O)₂R24', and S(O)₂N(R25')₂; and wherein aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three independently selected from R28; and wherein R10 and R11 optionally combine to form a 5 to 6 membered fused bicyclic ring with the phenyl to which they are bound;
- (k) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (l) R30 is selected from the group consisting of C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and wherein C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents each independently selected from R31;
- (m) R32 is selected from the group consisting of a bond, hydrogen, halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, and C₁-C₆ alkyloxy; and
- (n) — is optionally a bond to form a double bond at the indicated position.

Another embodiment of the present invention is a compound of the Formula III:



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

- (a) R1 is selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ alkenyl, C₁-C₈ heteroalkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and, wherein C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents independently selected from R1';
- (b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR12, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₀₋₄-alkyl, heteroaryl, heterocycloalkyl, C(O)R13, COOR14, OC(O)R15, OS(O)₂R16, N(R17)₂, NR18C(O)R19, NR20SO₂R21, SR22, S(O)R23, S(O)₂R24, and S(O)₂N(R25)₂; R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24 and R25 are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (c) R2 is selected from the group consisting of C₀-C₈ alkyl and C₁₋₄-heteroalkyl;

- (d) X is selected from the group consisting of a single bond, O, S, S(O)₂ and N;
- (e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R₃₀;
- (f) Y is selected from the group consisting of O, S, NH, C, and a single bond;
- (g) E is C(R₃)(R₄)A; wherein
- (i) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkynitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R⁷;
- (ii) each R⁷ is independently selected from the group consisting of hydrogen, C₁-C₆ haloalkyl, aryl C₀-C₄ alkyl and C₁-C₆ alkyl;
- (iii) R₃ is selected from the group consisting of C₁-C₅ alkyl, and C₁-C₅ alkoxy; and
- (iv) R₄ is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R₃ and R₄ are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R₂₆;
- with the proviso that when Y is O then R₄ is selected from the group consisting of C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R₃ and R₄ are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, cycloalkyl and aryl-alkyl are each optionally substituted with one to three each independently selected from R₂₆;

- (h) R8 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, and halo;
- (i) R9 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, halo, aryl-C₀-C₄ alkyl, heteroaryl, C₁-C₆ allyl, and OR29, and wherein aryl-C₀-C₄ alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C₁-C₄ alkyl;
- (j) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkylenyl, C₁-C₆ alkyl-COOR12'', C₀-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', OS(O)₂R16', N(R17')₂, NR18'C(O)R19', NR20'SO₂R21', SR22', S(O)R23', S(O)₂R24', and S(O)₂N(R25')₂; and wherein aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three independently selected from R28; and wherein R10 and R11 optionally combine to form a 5 to 6 membered fused bicyclic ring with the phenyl to which they are bound;
- (k) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (l) R30 is selected from the group consisting of C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and wherein C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents each independently selected from R31;
- (m) R32 is selected from the group consisting of a bond, hydrogen, halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, and C₁-C₆ alkylloxo; and
- (n) — is optionally a bond to form a double bond at the indicated position.

In one embodiment, the present invention also relates to pharmaceutical compositions comprising at least one compound of the present invention, or a pharmaceutically acceptable salt, solvate, hydrate, or stereoisomer thereof, and a pharmaceutically acceptable carrier.

In another embodiment, the present invention relates to a method of selectively modulating a PPAR delta receptor by contacting the receptor with at least one compound represented by Structural Formula I, or a pharmaceutically acceptable salt, solvate, hydrate, or stereoisomer thereof.

In another embodiment, the present invention relates to a method of modulating one or more of the PPAR alpha, beta, gamma, and/or delta receptors.

In a further embodiment, the present invention relates to a method of making a compound represented by Structural Formula I.

The compounds of the present invention are believed to be effective in treating and preventing Metabolic Disorder, Type II diabetes, hyperglycemia, hyperlipidemia, obesity, coagulopathy, hypertension, atherosclerosis, and other disorders related to Metabolic Disorder and cardiovascular diseases. Further, compounds of this invention can be useful for lowering fibrinogen, increasing HDL levels, treating renal disease, controlling desirable weight, treating demyelinating diseases, treating certain viral infections, and treating liver disease. In addition, the compounds can be associated with fewer clinical side effects than compounds currently used to treat such conditions.

DETAILED DESCRIPTION OF THE INVENTION

The terms used to describe the instant invention have the following meanings.

As used herein, the term "aliphatic linker" or "aliphatic group" is a non-aromatic, consisting solely of carbon and hydrogen and may optionally contain one or more units of unsaturation, e.g., double and/or triple bonds (also refer herein as "alkenyl" and "alkynyl"). An aliphatic or aliphatic group may be straight chained, branched (also refer herein as "alkyl") or cyclic (also refer herein as "cycloalkyl"). When straight chained or branched, an aliphatic group typically contains between about 1 and about 10 carbon atoms, more typically between about 1 and about 6 carbon atoms. When cyclic, an

aliphatic typically contains between about 3 and about 10 carbon atoms, more typically between about 3 and about 7 carbon atoms. Aliphatics are preferably C₁-C₁₀ straight chained or branched alkyl groups (i.e. completely saturated aliphatic groups), more preferably C₁-C₆ straight chained or branched alkyl groups. Examples include, but are not limited to methyl, ethyl, propyl, n-propyl, iso-propyl, n-butyl, sec-butyl, and tert-butyl. Additional examples include, but are not limited to, cyclopropyl, cyclopentyl, cyclohexyl, cyclohexyl and the like. Such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R30. It can be preferred that aliphatic linker is substituted with from zero to two substituents each independently selected from R30. Further, it may be preferred that one carbon of the aliphatic linker is replaced with an O, NH, or S.

The term "alkyl," unless otherwise indicated, refers to those alkyl groups of a designated number of carbon atoms of either a straight or branched saturated configuration. As used herein, "C₀ alkyl" means that there is no carbon and therefore represents a bond. Examples of "alkyl" include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl, pentyl, hexyl, isopentyl and the like. Alkyl as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above. As used herein, the term "alkyloxo" means an alkyl group of the designated number of carbon atoms with a "=O" substituent.

The term "alkenyl" or "alkylenyl" means hydrocarbon chain of a specified number of carbon atoms of either a straight or branched configuration and having at least one carbon-carbon double bond, which may occur at any point along the chain, such as ethenyl, propenyl, butenyl, pentenyl, vinyl, alkyl, 2-butenyl and the like. Alkenyl as defined above may be optionally substituted with designated number of substituents as set forth in the embodiment recited above.

The term "alkynyl" means hydrocarbon chain of a specified number of carbon atoms of either a straight or branched configuration and having at least one carbon-carbon triple bond, which may occur at any point along the chain. Example of alkynyl is acetylene. Alkynyl as defined above may be optionally substituted with designated number of substituents as set forth in the embodiment recited above.

The term "heteroalkyl" refers to a means hydrocarbon chain of a specified number

of carbon atoms wherein at least one carbon is replaced by a heteroatom selected from the group consisting of O, N and S.

The term "cycloalkyl" refers to a saturated or partially saturated carbocycle containing one or more rings of from 3 to 12 carbon atoms, typically 3 to 7 carbon atoms.

5 Examples of cycloalkyl includes, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and the like. "Cycloalkylaryl" means that an aryl is fused with a cycloalkyl, and "Cycloalkylaryl-alkyl" means that the cycloalkylaryl is linked to the parent molecule through the alkyl. Cycloalkyl as defined above may be optionally substituted with a designated number of substituents as set forth in the
10 embodiment recited above.

The term "halo" refers to fluoro, chloro, bromo and iodo.

The term "haloalkyl" is a C₁-C₆ alkyl group, which is substituted with one or more halo atoms selected from F, Br, Cl and I. An example of a haloalkyl group is trifluoromethyl (CF₃).

15 The term "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, and the like. Alkoxy as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

20 The term "haloalkyloxy" represents a C₁-C₆ haloalkyl group attached through an oxygen bridge, such as OCF₃. The "haloalkyloxy" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "aryl" includes carbocyclic aromatic ring systems (e.g. phenyl), fused
25 polycyclic aromatic ring systems (e.g. naphthyl and anthracenyl) and aromatic ring systems fused to carbocyclic non-aromatic ring systems (e.g., 1,2,3,4-tetrahydronaphthyl). "Aryl" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "arylalkyl" refers to an aryl alkyl group which is linked to the parent
30 molecule through the alkyl group, which may be further optionally substituted with a designated number of substituents as set forth in the embodiment recited above. When arylalkyl is arylC₀alkyl, then the aryl group is bonded directly to the parent molecule.

Likewise, arylheteroalkyl means an aryl group linked to the parent molecule through the heteroalkyl group.

The term "acyl" refers to alkylcarbonyl, arylcarbonyl, and heteroarylcarbonyl species.

5 The term "heteroaryl" group, as used herein, is an aromatic ring system having at least one heteroatom such as nitrogen, sulfur or oxygen and includes monocyclic, bicyclic or tricyclic aromatic ring of 5- to 14-carbon atoms containing one or more heteroatoms selected from the group consisting of O, N, and S. The "heteroaryl" as defined above may be optionally substituted with a designated number of substituents as set forth in the
10 embodiment recited above. Examples of heteroaryl are, but are not limited to, furanyl, indolyl, thienyl (also referred to herein as "thiophenyl") thiazolyl, imidazolyl, isoxazolyl, oxazolyl, pyrazolyl, pyrrolyl, pyrazinyl, pyridyl, pyrimidyl, pyrimidinyl and purinyl, cinnolinyl, benzofuranyl, benzothienyl, benzotriazolyl, benzoxazolyl, quinoline, isoxazolyl, isoquinoline and the like. The term "heteroarylalkyl" means that the
15 heteroaryl group is linked to the parent molecule through the alkyl portion of the heteroarylalkyl.

 The term "heterocycloalkyl" refers to a non-aromatic ring which contains one or more oxygen, nitrogen or sulfur and includes a monocyclic, bicyclic or tricyclic non-aromatic ring of 5 to 14 carbon atoms containing one or more heteroatoms selected from
20 O, N or S. The "heterocycloalkyl" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above. Examples of heterocycloalkyl include, but are not limited to, morpholine, piperidine, piperazine, pyrrolidine, and thiomorpholine. As used herein, alkyl groups include straight chained and branched hydrocarbons, which are completely saturated.

25 As used herein, the phrase "selectively modulate" means a compound whose EC50 for the stated PPAR receptor is at least ten fold lower than its EC50 for the other PPAR receptor subtypes.

 PPAR δ has been proposed to associate with and dissociate from selective co-repressors (BCL-6) that control basal and stimulated anti-inflammatory activities (Lee, C-
30 H. et al. Science 302:453-4572003). PPAR δ agonists are thought to be useful to attenuate other inflammatory conditions such as inflammation of the joints and connective tissue as

occurs in rheumatoid arthritis, related autoimmune diseases, osteoarthritis, as well as myriad other inflammatory diseases, Crohne's disease, and psoriasis.

When a compound represented by Structural Formula I has more than one chiral substituent it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be
5 separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated using methods familiar to the skilled artisan. The present invention includes each diastereoisomer of compounds of Structural Formula I and mixtures thereof.

Certain compounds of Structural Formula I may exist in different stable
10 conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present invention includes each conformational isomer of compounds of Structural Formula I and mixtures thereof.

Certain compounds of Structural Formula I may exist in zwitterionic form and the
15 present invention includes each zwitterionic form of compounds of Structural Formula I and mixtures thereof.

"Pharmaceutically-acceptable salt" refers to salts of the compounds of the Structural Formula I which are considered to be acceptable for clinical and/or veterinary use. Typical pharmaceutically-acceptable salts include those salts prepared by reaction of
20 the compounds of the present invention with a mineral or organic acid or an organic or inorganic base. Such salts are known as acid addition salts and base addition salts, respectively. It will be recognized that the particular counterion forming a part of any salt of this invention is not of a critical nature, so long as the salt as a whole is pharmaceutically-acceptable and as long as the counterion does not contribute undesired
25 qualities to the salt as a whole. These salts may be prepared by methods known to the skilled artisan.

The term, "active ingredient" means the compounds generically described by Structural Formula I as well as the stereoisomers, salts, solvates, and hydrates,

The term "pharmaceutically acceptable" means that the carrier, diluent, excipients
30 and salt are pharmaceutically compatible with the other ingredients of the composition. Pharmaceutical compositions of the present invention are prepared by procedures known in the art using well known and readily available ingredients.

"Preventing" refers to reducing the likelihood that the recipient will incur or develop any of the pathological conditions described herein. The term "preventing" is particularly applicable to a patient that is susceptible to the particular pathological condition.

5 "Treating" refers to mediating a disease or condition and preventing, or mitigating, its further progression or ameliorate the symptoms associated with the disease or condition.

"Pharmaceutically-effective amount" means that amount of active ingredient that will elicit the biological or medical response of a tissue, system, or mammal. Such an amount can be administered prophylactically to a patient thought to be susceptible to
10 development of a disease or condition. Such amount when administered prophylactically to a patient can also be effective to prevent or lessen the severity of the mediated condition. Such an amount is intended to include an amount which is sufficient to modulate a selected PPAR receptor or to prevent or mediate a disease or condition.
15 Generally, the effective amount of a Compound of Formula I will be between 0.02 through 5000 mg per day. Preferably the effective amount is between 1 through 1,500 mg per day. Preferably the dosage is from 1 through 1,000 mg per day. A most preferable the dose can be from 1 through 100 mg per day.

The desired dose may be presented in a single dose or as divided doses
20 administered at appropriate intervals.

A "mammal" is an individual animal that is a member of the taxonomic class Mammalia. The class Mammalia includes humans, monkeys, chimpanzees, gorillas, cattle, swine, horses, sheep, dogs, cats, mice, and rats.

Administration to a human is most preferred. The compounds and compositions
25 of the present invention are useful for the treatment and/or prophylaxis of cardiovascular disease, for raising serum HDL cholesterol levels, for lowering serum triglyceride levels and for lower serum LDL cholesterol levels. Elevated triglyceride and LDL levels, and low HDL levels, are risk factors for the development of heart disease, stroke, and circulatory system disorders and diseases.

30 Further, the compound and compositions of the present invention may reduce the incidence of undesired cardiac events in patients. The physician of ordinary skill will

know how to identify humans who will benefit from administration of the compounds and compositions of the present invention.

The compounds and compositions of the present invention are also useful for treating and/or preventing obesity.

5 Further, these compounds and compositions are useful for the treatment and/or prophylaxis of non-insulin dependent diabetes mellitus (NIDDM) with reduced or no body weight gains by the patients. Furthermore, the compounds and compositions of the present invention are useful to treat or prevent acute or transient disorders in insulin sensitivity, such as sometimes occur following surgery, trauma, myocardial infarction, and the like. The physician of ordinary skill will know how to identify humans who will benefit from administration of the compounds and compositions of the present invention.

10 The present invention further provides a method for the treatment and/or prophylaxis of hyperglycemia in a human or non-human mammal which comprises administering an effective amount of active ingredient, as defined herein, to a hyperglycemic human or non-human mammal in need thereof.

15 The invention also relates to the use of a compound of Formula I as described above, for the manufacture of a medicament for treating a PPAR receptor mediated condition.

20 A therapeutically effective amount of a compound of Structural Formula I can be used for the preparation of a medicament useful for treating Metabolic Disorder, diabetes, treating obesity, lowering triglyceride levels, lowering serum LDL levels, raising the plasma level of high density lipoprotein, and for treating, preventing or reducing the risk of developing atherosclerosis, and for preventing or reducing the risk of having a first or subsequent atherosclerotic disease event in mammals, particularly in humans. In general, a therapeutically effective amount of a compound of the present invention typically reduces serum triglyceride levels of a patient by about 20% or more, and increases serum HDL levels in a patient. Preferably, HDL levels will be increased by about 30% or more. In addition, a therapeutically effective amount of a compound, used to prevent or treat NIDDM, typically reduces serum glucose levels, or more specifically HbA1c, of a patient by about 0.7% or more.

30 When used herein Metabolic Syndrome includes pre-diabetic insulin resistance syndrome and the resulting complications thereof, insulin resistance, non-insulin

dependent diabetes, dyslipidemia, hyperglycemia obesity, coagulopathy, hypertension and other complications associated with diabetes. The methods and treatments mentioned herein include the above and encompass the treatment and/or prophylaxis of any one of or any combination of the following: pre-diabetic insulin resistance syndrome, the resulting
5 complications thereof, insulin resistance, Type II or non-insulin dependent diabetes, dyslipidemia, hyperglycemia, obesity and the complications associated with diabetes including cardiovascular disease, especially atherosclerosis. In addition, the methods and treatments mentioned herein include the above and encompass the treatment and/or prophylaxis of any one of or any combination of the following inflammatory and
10 autoimmune diseases: adult respiratory distress syndrome, rheumatoid arthritis, demyelinating disease, Chrohne's disease, asthma, systemic lupus erythematosus, psoriasis, and bursitis.

The compositions are formulated and administered in the same general manner as detailed herein. The compounds of the instant invention may be used effectively alone or
15 in combination with one or more additional active agents depending on the desired target therapy. Combination therapy includes administration of a single pharmaceutical dosage composition which contains a compound of Structural Formula I, a stereoisomer, salt, solvate and/or hydrate thereof ("Active Ingredient") and one or more additional active agents, as well as administration of a compound of Active Ingredient and each active
20 agent in its own separate pharmaceutical dosage formulation. For example, an Active Ingredient and an insulin secretagogue such as biguanides, thiazolidinediones, sulfonylureas, insulin, or α -glucosidase inhibitors can be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent administered in separate oral dosage formulations. Where separate dosage formulations
25 are used, an Active Ingredient and one or more additional active agents can be administered at essentially the same time, i.e., concurrently, or at separately staggered times, i.e., sequentially; combination therapy is understood to include all these regimens.

An example of combination treatment or prevention of atherosclerosis may be wherein an Active Ingredient is administered in combination with one or more of the
30 following active agents: antihyperlipidemic agents; plasma HDL-raising agents; antihypercholesterolemic agents, fibrates, vitamins, aspirin, and the like. As noted above,

the Active Ingredient can be administered in combination with more than one additional active agent.

Another example of combination therapy can be seen in treating diabetes and related disorders wherein the Active Ingredient can be effectively used in combination with, for example, sulfonylureas, biguanides, thiazolidinediones, α -glucosidase inhibitors, other insulin secretagogues, insulin as well as the active agents discussed above for treating atherosclerosis.

The Active Ingredients of the present invention, have valuable pharmacological properties and can be used in pharmaceutical compositions containing a therapeutically effective amount of Active Ingredient of the present invention, in combination with one or more pharmaceutically acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, fillers, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, wetting agents, binders, disintegrating agents, encapsulating material and other conventional adjuvants. Proper formulation is dependent upon the route of administration chosen. Pharmaceutical compositions typically contain from about 1 to about 99 weight percent of the Active Ingredient of the present invention.

Preferably, the pharmaceutical formulation is in unit dosage form. A "unit dosage form" is a physically discrete unit containing a unit dose, suitable for administration in human subjects or other mammals. For example, a unit dosage form can be a capsule or tablet, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the Active Ingredient of the present invention, calculated to produce the desired therapeutic effect, in association with one or more pharmaceutically-acceptable excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1500 milligrams or more according to the particular treatment involved. It may be preferred that the unit dosage is from about 1 mg to about 1000 mg.

The dosage regimen utilizing the compounds of the present invention is selected by one of ordinary skill in the medical or veterinary arts, in view of a variety of factors, including, without limitation, the species, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed, and the like.

Advantageously, compositions containing the compound of Structural Formula I or the salts thereof may be provided in dosage unit form, preferably each dosage unit containing from about 1 to about 500 mg be administered although it will, of course, readily be understood that the amount of the compound or compounds of Structural
5 Formula I actually to be administered will be determined by a physician, in the light of all the relevant circumstances.

Preferably, the compounds of the present invention are administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day. Where delivery is via transdermal forms, of course, administration is
10 continuous.

Suitable routes of administration of pharmaceutical compositions of the present invention include, for example, oral, eyedrop, rectal, transmucosal, topical, or intestinal administration; parenteral delivery (bolus or infusion), including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraven-tricular,
15 intravenous, intraperitoneal, intranasal, or intraocular injections. The compounds of the invention can also be administered in a targeted drug delivery system, such as, for example, in a liposome coated with endothelial cell-specific antibody.

Solid form formulations include powders, tablets and capsules.

Sterile liquid formulations include suspensions, emulsions, syrups, and elixirs.

20 Pharmaceutical compositions of the present invention can be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

The following pharmaceutical formulations 1 and 2 are illustrative only and are
25 not intended to limit the scope of the invention in any way.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity
	<u>(mg/capsule)</u>
Active Ingredient	250

	Quantity (mg/capsule)
Starch, dried	200
Magnesium stearate	<u>10</u>
Total	460 mg

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
Active Ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	<u>5</u>
Total	665 mg

- 5 The components are blended and compressed to form tablets each weighing 665 mg.

10 In yet another embodiment of the compounds of the present invention, the compound is radiolabelled, such as with carbon-14, or tritiated. Said radiolabelled or tritiated compounds are useful as reference standards for in vitro assays to identify new selective PPAR receptor agonists.

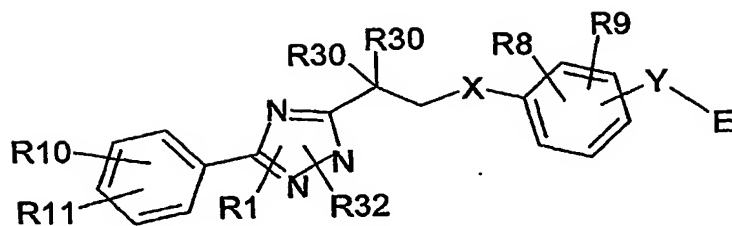
15 The compounds of the present invention can be useful for modulating insulin secretion and as research tools. Certain compounds and conditions within the scope of this invention are preferred. The following conditions, invention embodiments, and compound characteristics listed in tabular form may be independently combined to produce a variety of preferred compounds and process conditions. The following list of embodiments of this invention is not intended to limit the scope of this invention in any way.

Some preferred characteristics of compounds of formula I are:

- 20 (a) R3 is methyl;

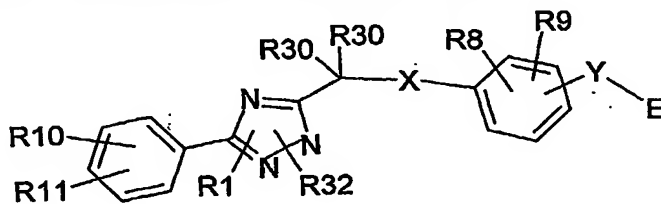
- 5 (b) R4 is hydrogen;
(c) R3 and R4 are each hydrogen;
(d) R3 and R4 are each methyl;
(e) A is carboxyl;
(f) X is -O-;
(g) X is -S-;
(h) X is a bond;
(i) U is CH;
(j) U is CH₂CH;
10 (k) U is CH₂N(R30)CH₂;
(l) U is CH₂OCH₂;
(m) U is CH₂CH₂CH₂;
(n) W is N;
(o) W is O;
15 (p) W is S;
(q) R30 is CH₃;
(r) R9 is methyl;
(s) R9 is hydrogen;
(t) R9 is C₁-C₃ alkyl;
20 (u) R8 is methyl;
(v) R8 and R9 are each hydrogen;
(w) R10 is CF₃;
(x) R10 is haloalkyl;
(y) R10 is haloalkyloxy;
25 (z) R11 is hydrogen
(aa) R10 and R11 are each hydrogen;
(bb) R11 is haloalkyl;
(cc) R10 and R11 combine to form a fused bicyclic;
(dd) R10 and R11 combine to form a naphthyl substituent with the
30 phenyl to which they are attached;
(ee) R1 is optionally substituted C2-C3 arylalkyl;

- (ff) R1 is substituted C2 arylalkyl;
- (gg) ---- in the five membered ring each form a double bond at the designated position in Formula I;
- 5 (hh) R1 is C₁-C₄ alkyl;
- (ii) R32 is hydrogen;
- (jj) R2 is a bond;
- (kk) R2 is C₁-C₂ alkyl;
- (ll) Y is O;
- (mm) Y is S;
- 10 (nn) Y is C;
- (oo) Y is C, NH, or a bond;
- (pp) E is C(R3)(R4)A;
- (qq) R3 is hydrogen;
- (rr) R3 is C₁-C₂ alkyl;
- 15 (ss) R4 is C₁-C₂ alkyl;
- (tt) R3 and R4 are each hydrogen;
- (uu) R3 and R4 are each methyl;
- (vv) A is COOH;
- (ww) Aliphatic linker is saturated;
- 20 (xx) Aliphatic linker is substituted with C₁-C₃ alkyl;
- (yy) Aliphatic linker is substituted with from one to three substituents each independently selected from R30;
- (zz) Aliphatic linker is substituted with from one to two substituents each independently selected from R30;
- 25 (aaa) Aliphatic linker is C₁-C₃ alkyl;
- (bbb) Aliphatic linker is C₁-C₂ alkyl;
- (ccc) Aliphatic linker is C₁-C₃ alkyl and one carbon is replaced with an -O-;
- (ddd) A compound of Formula IV:



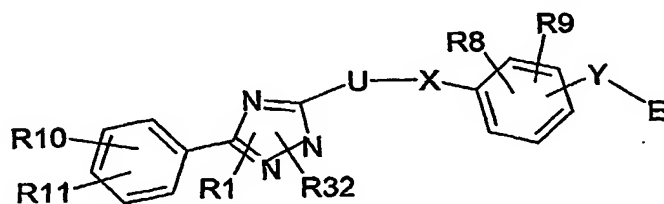
IV;

(eee) A compound of Structural Formula V:



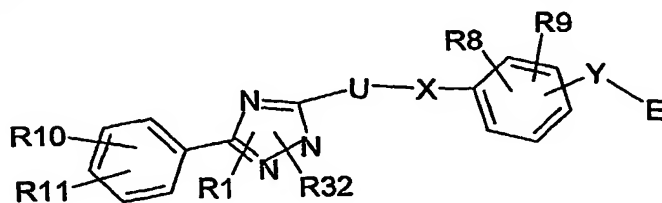
V;

(fff) A compound of Structural Formula VI:



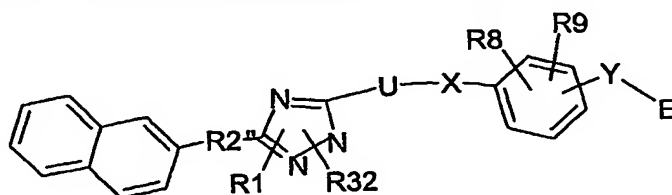
VI;

(ggg) A compound of Structural Formula VII:



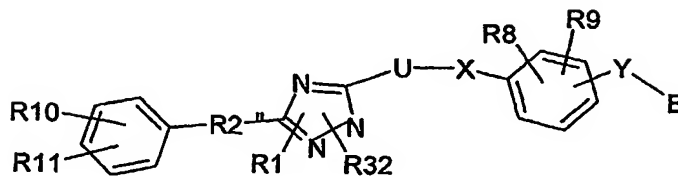
VII;

(hhh) A compound of Structural Formula VIII:



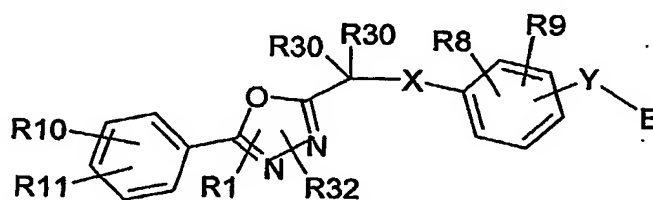
VIII;

(iii) A compound of Structural Formula IX:



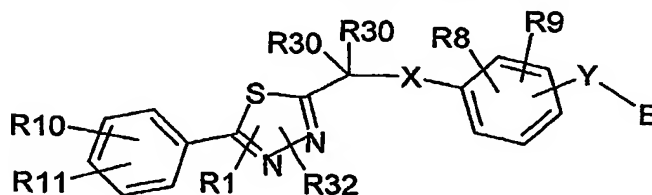
IX;

(jjj) A compound of Structural Formula X:



X;

(kkk) A compound of Structural Formula XI:



XI;

(III) A compound of Structural Formula IX:

(mmm) Aryl is a phenyl group;

(nnn) Aryl is a naphthyl group;

(ooo) A compound of Formula I that selectively modulates a delta receptor;

(ppp) An Active Ingredient, as described herein, that is a PPAR coagonist that modulates a gamma receptor and a delta receptor;

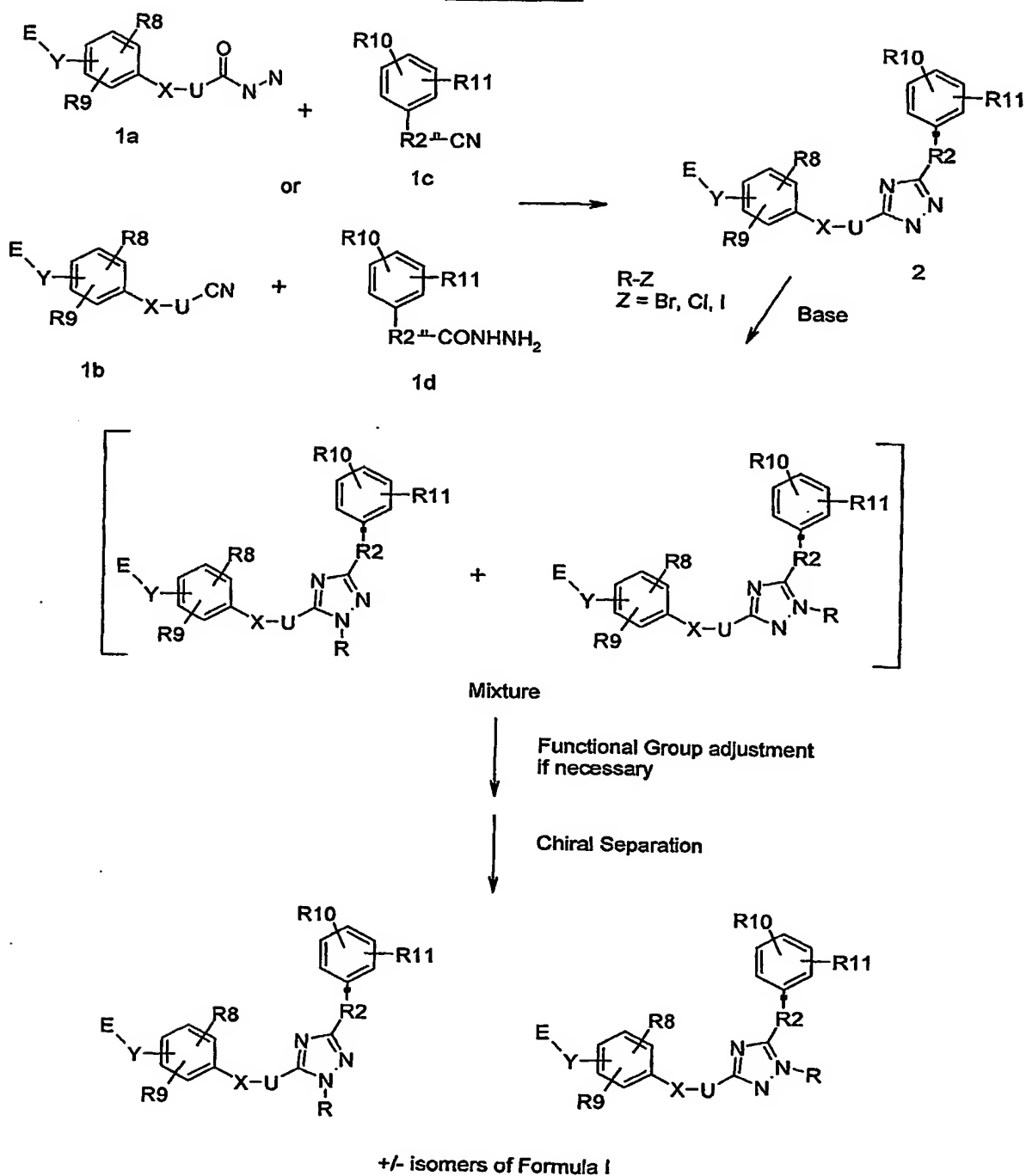
(qqq) An Active Ingredient, as described herein, for use in the treatment of cardiovascular disease;

(rrr) An Active Ingredient, as described herein, for use in the treatment of Metabolic Disorder;

(sss) An Active Ingredient for use in the control of obesity;

- (ttt) An Active Ingredient for use in treating diabetes;
- (uuu) An Active Ingredient that is a PPAR receptor agonist;
- (vvv) A compound of Formula I selected from the group consisting of
2-Methyl-2-{4-[3-(5-naphthalen-2-ylmethyl-2H-[1,2,4]triazol-
3-yl)-phenoxy}propionic acid.

Scheme 1



Compounds of Formula I are prepared by the reaction of either a carbonyl
 5 hydrazone 1a in the presence of a carbonitrile 1b or of a carbonyl hydrazone 1d in the
 presence of a carbonitrile 1c to give intermediates 2. The reaction to form the triazole

core 2 occurs in the presence of a strong base, e.g., sodium, lithium, or potassium alkoxides or sodium, lithium or potassium hydroxides in a polar protic solvent such as lower molecular weight alkanols, e.g., methanol, ethanol, or n- or i-propanol at reaction temperatures from room temperature to the reflux temperature of the mixture. Compound 2 is alkylated with a primary or secondary alkyl halide R-Z, where R includes the definition of both R³² and R¹ in the presence of a base, e.g., sodium, lithium, or potassium bicarbonate or carbonate in a polar aprotic solvent, e.g., acetonitrile, acetone, or DMF at from room temperature to the reflux temperature of the mixture. Catalytic KI may be added to facilitate the overall alkylation by in situ replacement of R-Z, if Z is Cl or Br, to the more reactive R-I alkylation reagent. The alkylation with R give a mixture of regio and therefore optical isomers of Formula I.

Since racemic mixtures of Formula I are separated and isolated by chiral chromatography to pure isomers, at times, the racemic mixtures of Formula I are required to have functional group adjustments, perhaps, lending the mixtures to optimum separation in the chiral chromatography procedure. Functional group adjustments anticipated here and appreciated by one skilled in manipulations of organic reactions include manipulations of carboxylic acid derivatives, if applicable, to either esters of low molecular weight such as methyl or ethyl esters or to esters with steric hindrance such as t-butyl esters. Alternately as appreciated by one skilled in the execution of synthetic methodologies, ester functionalities, if applicable, may be adjusted to the free carboxylic acids by saponification of lower molecular weight esters with sodium, lithium or potassium hydroxides in a polar protic solvents, such as, methanol or ethanol, or strong acid hydrolysis of hindered esters, e.g., t-butyl esters with TFA in a weakly polar aprotic solvent such as methylene chloride or dichloroethane.

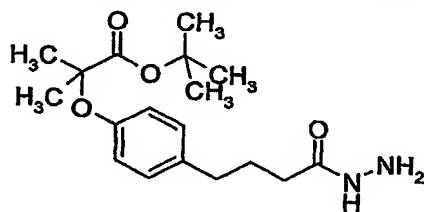
Other functional group manipulations include the conversion of ketones or aldehydes, if applicable, to ketals and acetals, with lower molecular weight alkane-diols and strong acid, e.g., tosic acid and sulfuric acid. Alternately, acetals and ketals, if present, may be converted to the corresponding carbonyl compound with strong acid and hydrated lower alkanols or with BBr₃ in dichloromethane or dichloroethane.

The starting materials for the above scheme may often be commercially available, particularly, for carbonitrile compounds 1c and 1b. Other carbonitriles of formula 1c and 1b may be prepared, as is common to one skilled in the art of organic manipulations, from

1) commercially available or known carboxylic acids by conversion to primary amides followed by dehydration with a Vilsmeier reagent or 2) commercially available or known carboxaldehydes by conversion to oximes followed by dehydration with a Vilsmeier reagent.

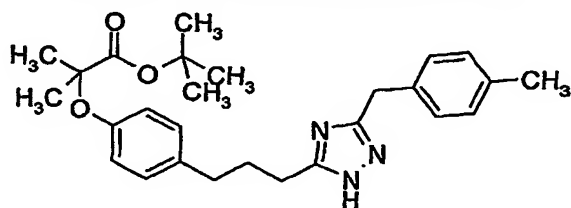
- 5 Hydrazones of the formula 1a and 1d are prepared from the corresponding carboxylic acids or acid halides and hydrazine in dichloromethane or dichloroethane in the presence of base such as, pyridine, triethylamine, or sodium, lithium, or potassium bicarbonate or carbonate. A particularly useful reference for the preparation of 1a or 1d is Xu, Yanping, et. al. J. Med. Chem. 46(24) (2003) p. 5121-5124, where analogous
10 reactions may be applied to the synthesis of 1a or 1d using commercially available or known carboxylic acids.

PREPARATION 1 (COMPOUND 1)



15

EXAMPLE 2A (COMPOUND 2A)

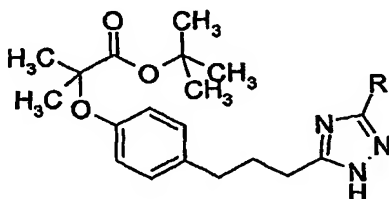


- 20 Take up the compound or preparation 1 [Xu, et. al. Loc. Cit. (2003)] (1.34 gm, 4 mmol) in methanol (30 mL). To this solution, add 4-methylbenzyl nitrile (1.04 gm, 8 mmole), followed by sodium methoxide (75 mg). Heat the reaction at reflux (~80°C) with stirring for 24 h. Dilute the mixture with ethyl acetate (50 mL). Wash the ethyl acetate with water (3 x 60 mL), dried (Na₂SO₄), and concentrate on a rotovap to give an oily residue. Purify the residue on a silica column to give 2a as an oil (670 mg).
m/z: M+1 450.

25

EXAMPLES 2B-2D

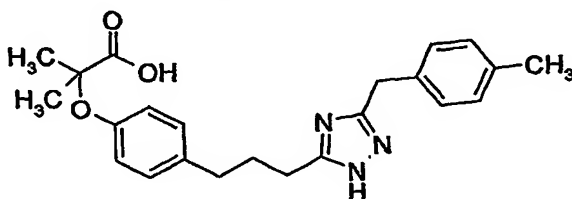
Synthesize Examples 2b to 2d shown in the following Table according to the procedure for example 2a, from preparation 1 using appropriate nitrile shown in Table below.



5

Example	R	Nitrile Used	(m/z) M+1
2b	Phenethyl	2-Phenylpropionitrile	450
2c	Naphthylmethyl	2-Naphthylacetonitrile	486
2d	3-(4-Chlorophenyl)-3-ethoxypropyl	4-(4-Chlorophenyl)-4-ethoxybutyronitrile	542

EXAMPLE 3A

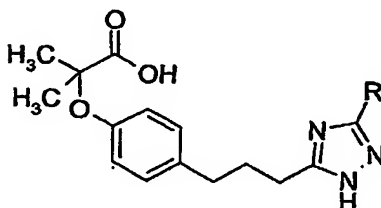


Take up the compound of example 2a (120 mg) in 50% TFA-dichloromethane (5 mL). Stir this mixture at room temperature for 18 h. Remove the solvent on a rotovap and dry the residue under high vacuum to give an oil (101 mg).
m/z: 394 (M+1).

10

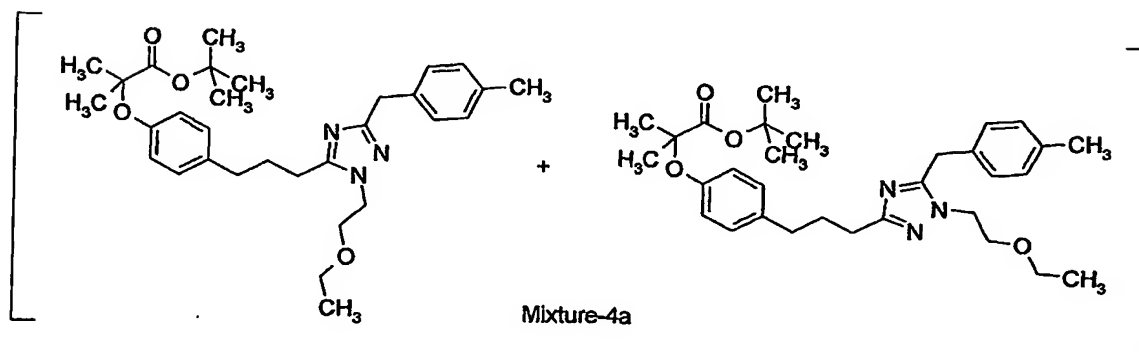
EXAMPLES 3B-3D

Synthesize examples 3b to 3c shown in the following Table according to the procedure for 3a, using TFA mediated hydrolysis of appropriate *t*-butyl esters of examples 2b to 2d.



Example	R	(m/z) M+1
3b	Phenethyl	394
3c	Naphthylmethyl	430
3d	3-(4-Chlorophenyl)-3-ethoxypropyl	486

EXAMPLE 4A



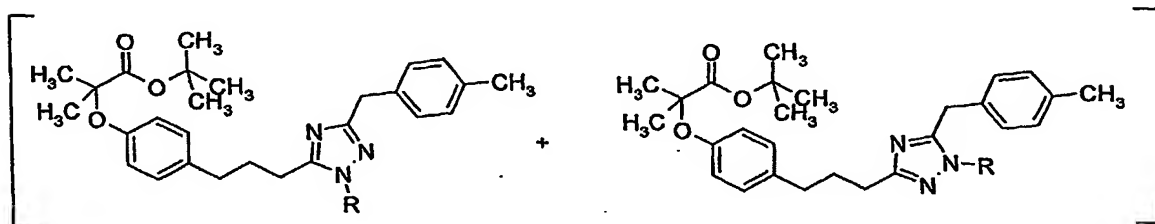
10 Add 2-ethoxyethylbromide (0.1 mL) to a solution of 2a (70 mg) in anhydrous DMF (1.5 mL) followed by anhydrous powdered K_2CO_3 . Heat the reaction mixture at 50°C with stirring for 18 h. Dilute the mixture with ethyl acetate (30 mL) and wash the ethyl acetate with water (3 x 30 mL). Dry the ethyl acetate layer (Na_2SO_4) and concentrate on a rotovap to give an oily residue. Purify the residue on a silica column to give approximate 40-60 regio-isomeric mixture of example 4a as an oil (62 mg).

15 m/z: 522 (M+1).

EXAMPLES 4B TO 4F

Synthesize Compounds **4b** to **4f** shown in the following Table according to the procedure for **4a** from **2a** using appropriate alkylbromide as shown in Table below.

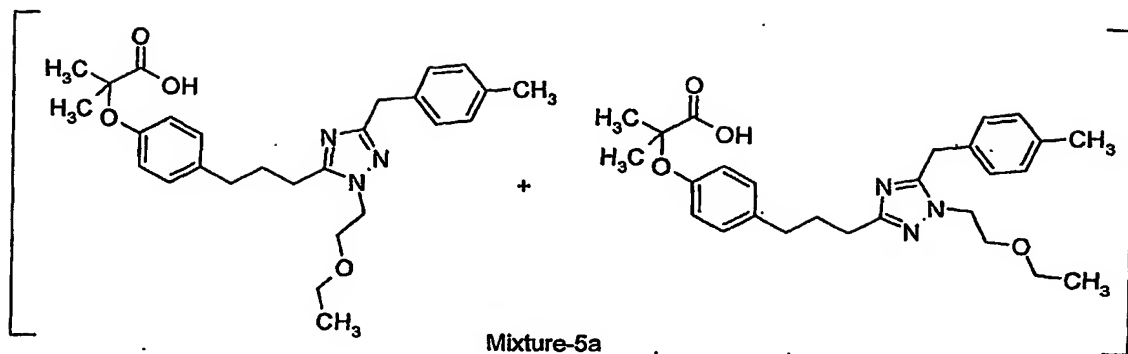
5



Mixture-4b to 4e

Example	R	Alkylbromide Used	(m/z) M+1
4b	2-(2-methoxy)ethoxyethyl	2-(2-methoxy)ethoxyethylbromide	552
4c	3-tetrahydropyranoxypropyl	3-tetrahydropyranoxypropyl bromide	592
4d	6-tetrahydropyranoxyhexyl	6-tetrahydropyranoxyhexylbromide	634
4e	4- <i>t</i> -butylbenzyl	4- <i>t</i> -butylbenzylbromide	596
4f	2-Oxobutyl	1-Bromobutan-2-one	520

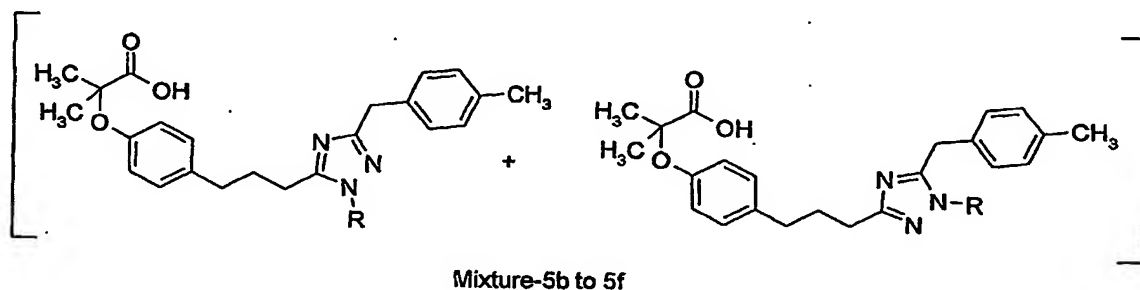
EXAMPLE 5A



Take up the triazole **mixture-4a** (61 mg) in 50% TFA-dichloromethane (4 mL). Stir this mixture at room temperature for 4 h. Remove the solvent on a rotovap and dry the residue under high vacuum to give regioisomeric **mixture 5a** an oil (30 mg). m/z : 466 (M+1)

EXAMPLES 5B TO 5F

10 Synthesize Compounds **5b** to **5f** shown in the following Table according to the procedure for **5a**, by TFA mediated hydrolysis of *tert*-butyl esters **4e** to **4c**.



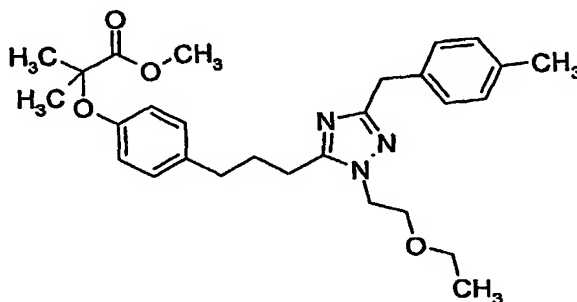
Example	R	(m/z) M+1
5b	2-(2-methoxy)ethoxyethyl	496
5c	3-hydroxypropyl	452
5d	6-hydroxyhexyl	494
5e	4- <i>t</i> -butylbenzyl	540

Example	R	(m/z) M+1
5f	2-Oxobutyl	464

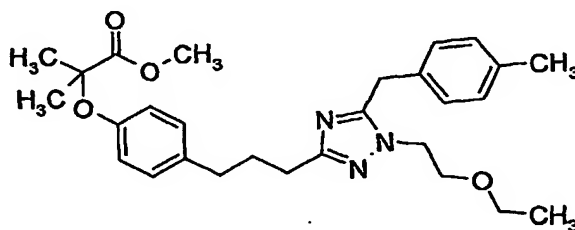
EXAMPLES 6 AND 7

5 Add conc. H₂SO₄ to a solution of mixture-5a (70 mg) in methanol (25 mL). Stir the reaction mixture at room temperature for 18 h. Remove the solvent to a small volume and dilute the residue with ethyl acetate (30 mL). Wash the ethyl acetate layer with water (3 x 30 mL), dry (Na₂SO₄), and concentrate on a rotovap to give an oily residue (71 mg). Purify the residue on a chiral HPLC column to give pure 6 and 7. 6: (15 mg), m/z: 480 (M+1).

10

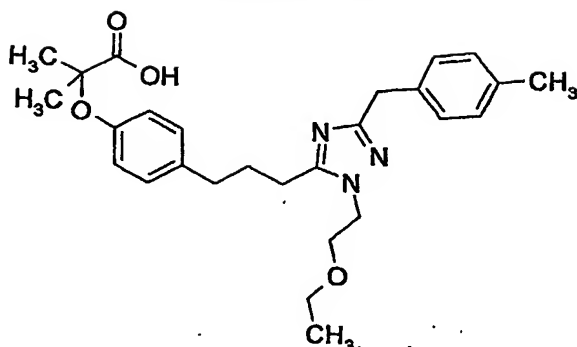


7: (19 mg), m/z: 480 (M+1).



15

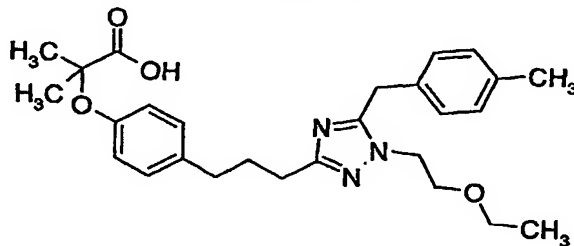
EXAMPLE 8



Take up the triazole ester 6 (15 mg) in methanol (2 mL). Add 2N aqueous NaOH (1mL) to this solution. Stir the mixture at room temperature for 2 h. Evaporate the solvent on the rotovap and dissolve the residue in water (5 mL). Acidify the solution to pH ~3 with 0.1 M aqueous HCl to give a milky solution. Extract the mixture with CH₂Cl₂ (3 x 10 mL). Dry the combined CH₂Cl₂ layers (Na₂SO₄), concentrate on a rotovap, and then dry under high vacuum to give example 8 (11 mg).
m/z: 466 (M+1).

10

EXAMPLE 9

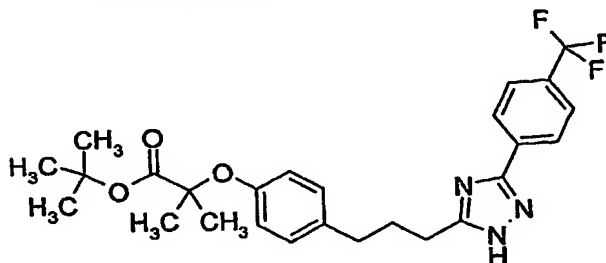


Synthesize example 9 according to the procedure for example 8 by NaOH mediated hydrolysis of ester example 6. m/z: 466 (M+1).

15

EXAMPLE 10

2-Methyl-2-(4-{3-[5-(4-trifluoromethyl-phenyl)-2H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-propionic acid tert-butyl ester

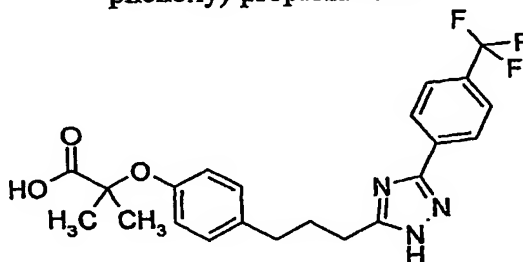


5 Add 4-(trifluoromethyl)benzonitrile (0.51 g, 3.0 mol) and potassium *tert*-butoxide (0.023 g, 0.21 mmol) to a solution of 2-[4-(3-Hydrazinocarbonyl-propyl)-phenoxy]-2-methyl-propionic acid tert-butyl ester (0.5 g, 1.5 mmol) in MeOH (5 mL). Stir the mixture at reflux overnight. Add an additional 0.2 equivalents of potassium *tert*-butoxide and stir the reaction for 24 h. Quench the crude with water, remove the MeOH in vacuo, and stir the reaction for 24 h. Quench the crude with water, remove the MeOH in vacuo, and extract the aqueous layer with EtOAc. Separate the organic layer, dry with MgSO₄,
10 and concentrate in vacuo. Purify the crude by Biotage (Hexane/EtOAc 4:1) yielding 0.32 g (44 %) of the title compound, example 10 as a pale yellow oil. MS Data (ES⁺) m/z 490.6 [M + H]

15

EXAMPLE 11

2-Methyl-2-(4-{3-[5-(4-trifluoromethyl-phenyl)-2H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-propionic acid

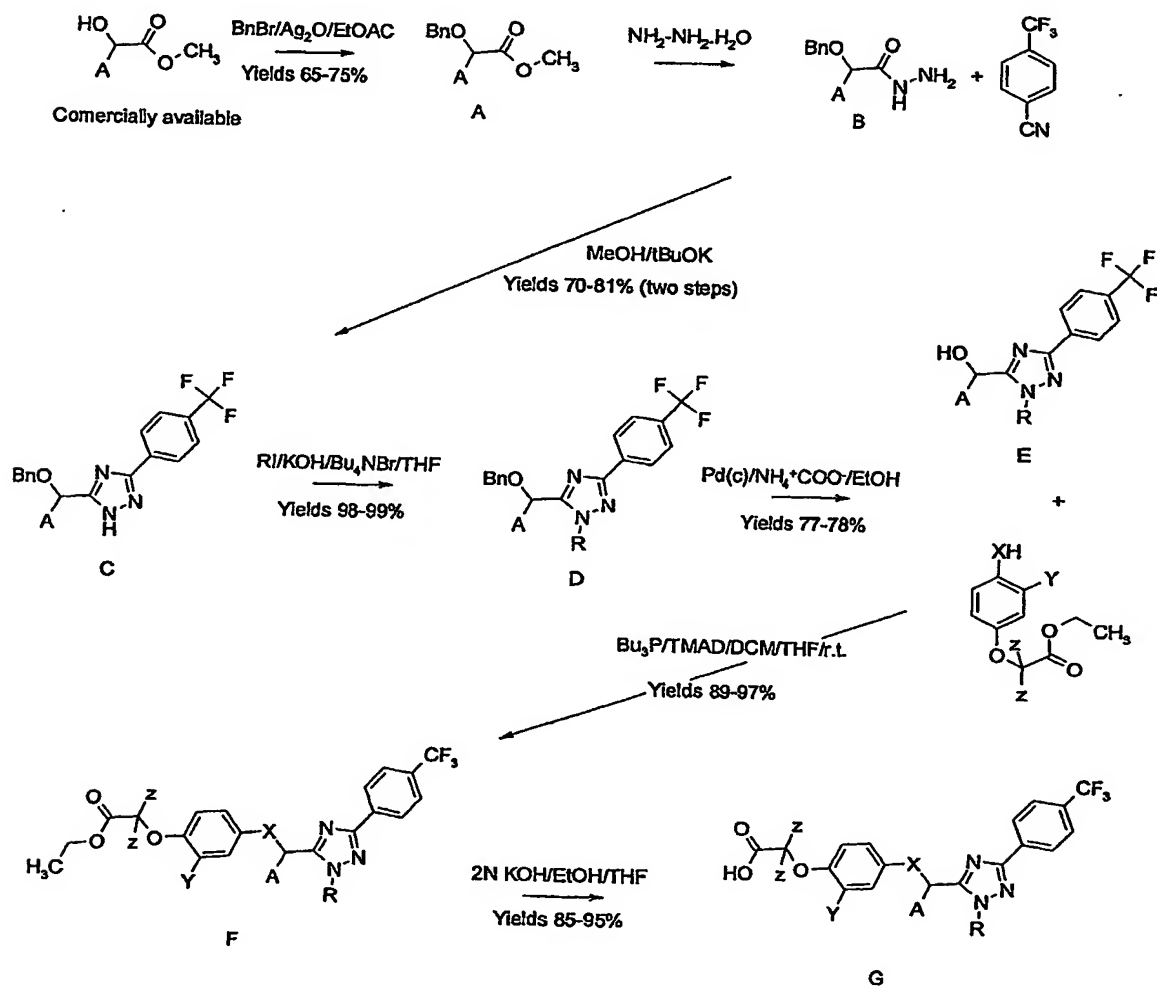


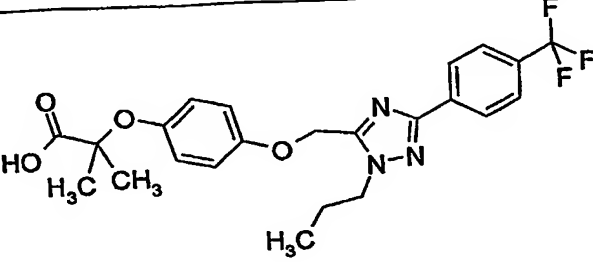
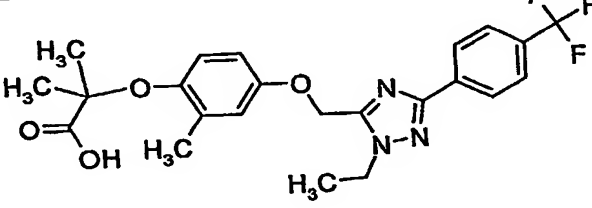
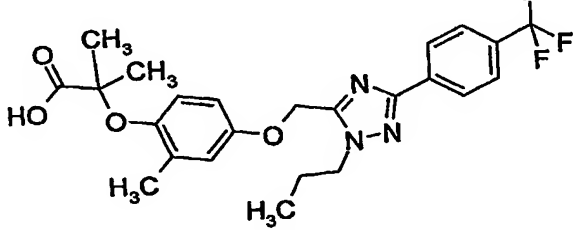
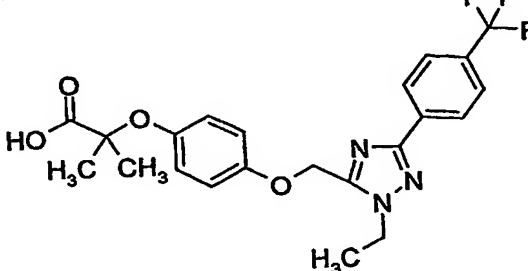
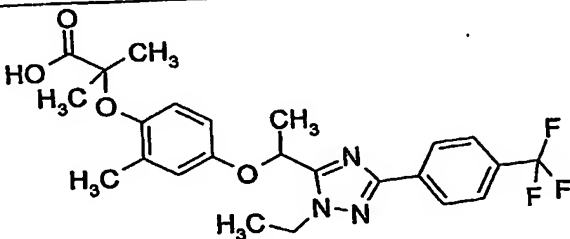
20 Add TFA (0.31 mL, 3.98 mmol) to a solution of example 10 (0.65 g, 1.33 mmol) in CH₂Cl₂ (6.5 ml). Stir the mixture at room temperature overnight. By TLC, a significant amount of starting material remains. Remove the solvent and residual TFA in vacuo. Purify the crude material by flash column chromatography (Hexane/EtOAc 2:1

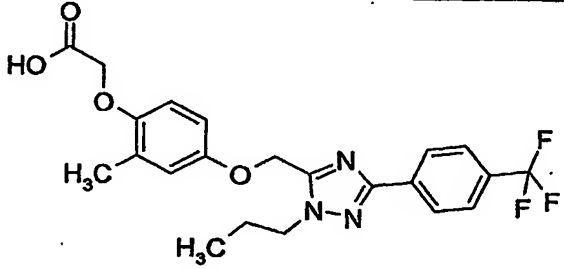
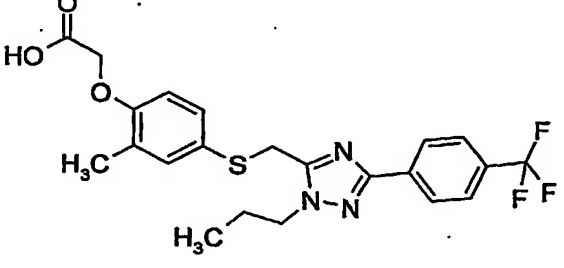
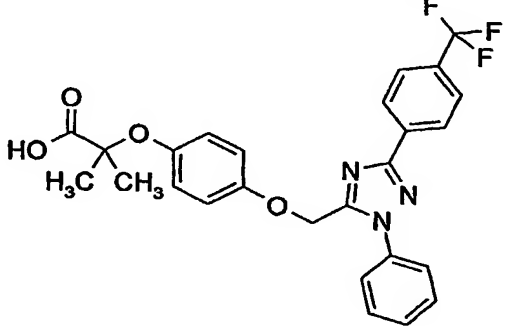
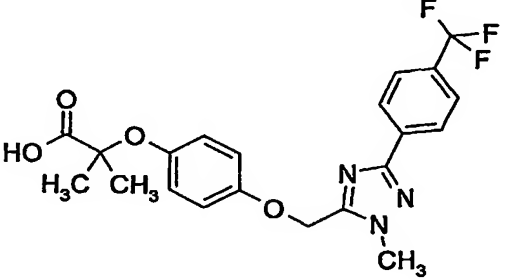
and 1:1) yielding 0.16 g (28 %) of example 10 as a white solid, and 0.4 g of the starting material recovered. MS Data (ES⁺) m/z 434.3 [M + H].

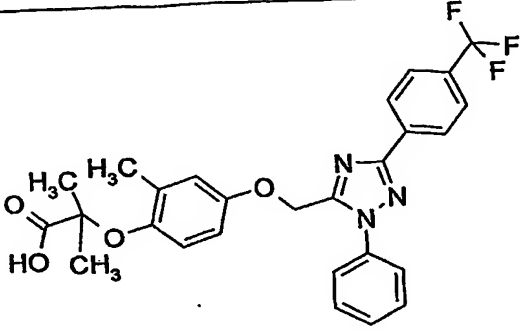
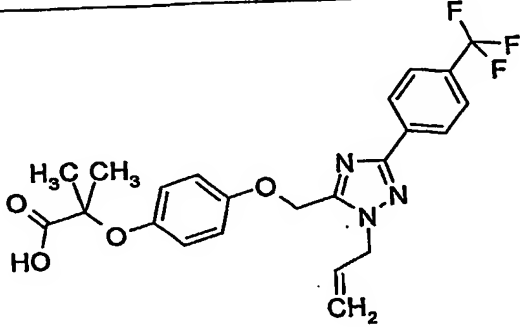
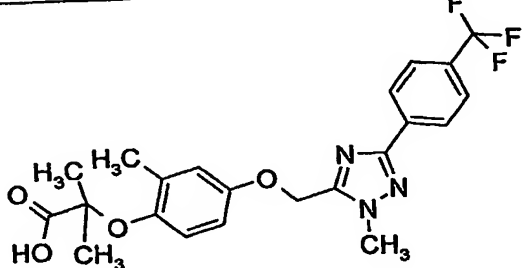
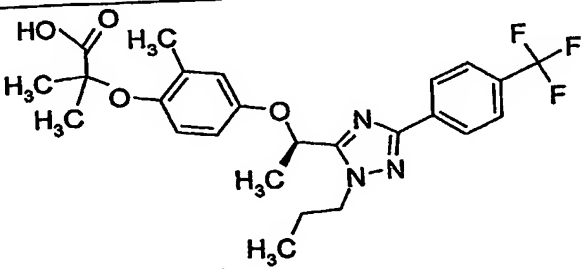
SCHEME 2

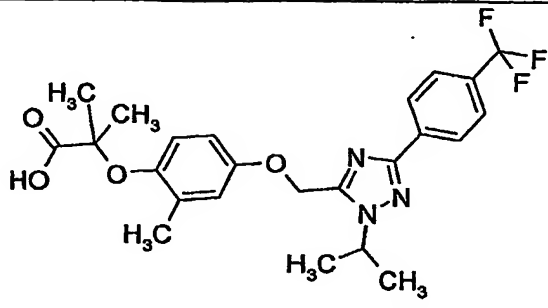
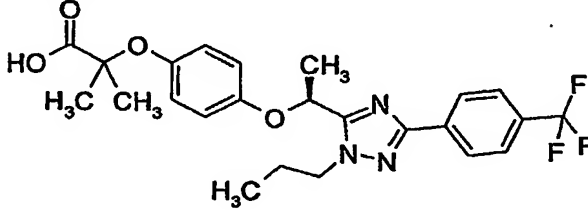
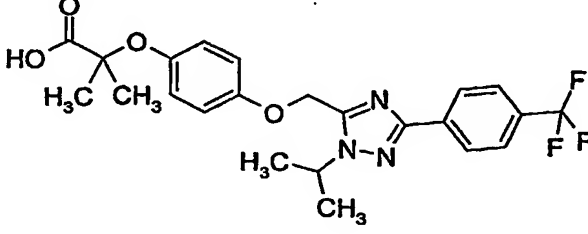
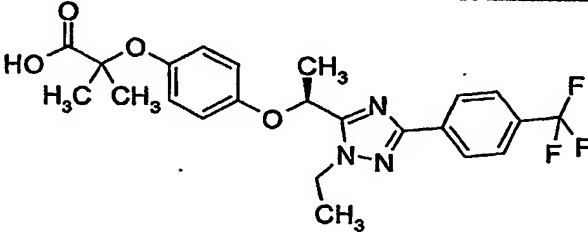
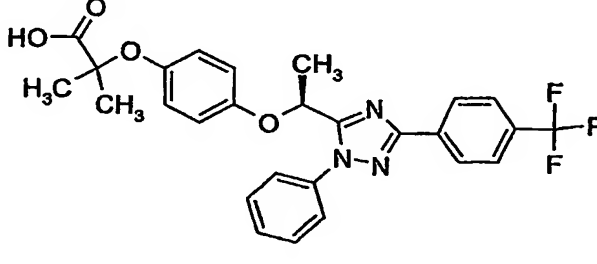
5

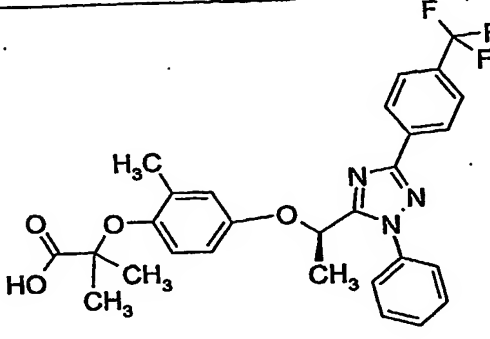
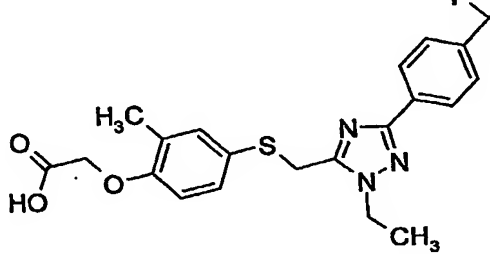
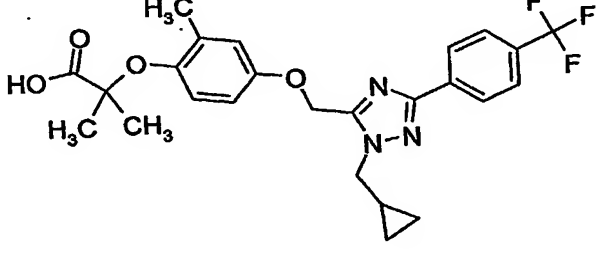
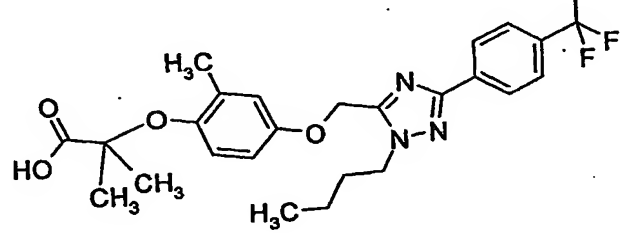


Example	Structure	LC/MS [M + 1]
12		464.4
13		464.2
14		478.1
15		450.4
16		478.3

Example	Structure	LC/MS [M + 1]
17		450.0
18		466.0
19		498.0
20		436.1

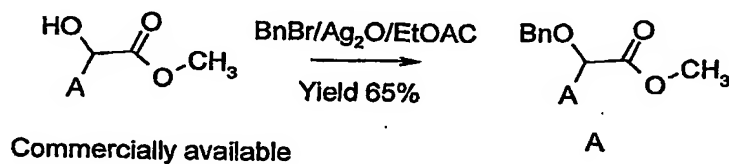
Example	Structure	LC/MS [M + 1]
21		511.9
22		475.9
23		450.1
24		492.3

Example	Structure	LC/MS [M + 1]
25		478.3
26		478.1
27		464.2
28		464.2
29		512.2

Example	Structure	LC/MS [M + 1]
30		526.2
31		452.2
32		490.1
33		492.3

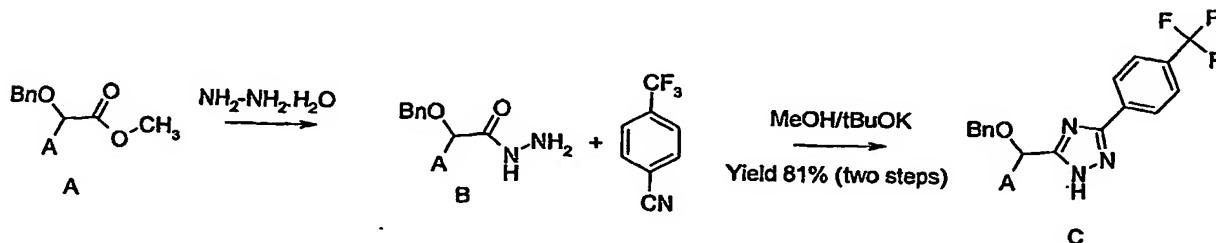
Example	Structure	LC/MS [M + 1]
34		494.2

GENERAL PROCEDURE FOR SCHEME 2



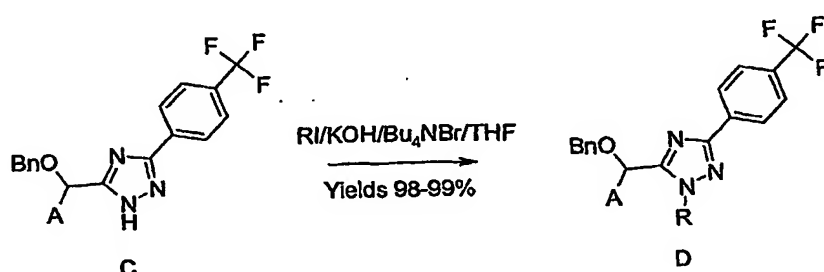
5

Add BnBr (1.1 mmol) and Ag₂O (1.1 mmol) to a solution of commercial starting material (1.0 mmol) in EtOAc (5 mL/mmol). Reflux the mixture overnight. Follow the reaction by TLC (Hexane /EtOAc 1:1). Filter the reaction through celite and remove the solvent under vacuum. Purify the crude material by flash chromatography (Hexane and
 10 Hexane/EtOAc 20%) to obtain a compound of formula A of scheme 2 as a colorless oil.



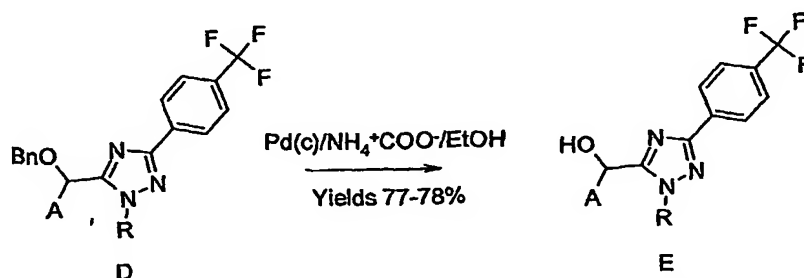
Dissolve the benzyl derivative compound of formula A of scheme 2 (1.0 mmol) in EtOH (0.8 M). Then, add hydrazine monohydrate (3.0 mmol). Stir the mixture at room
 15 temperature overnight. Follow the reaction by TLC (hexane/EtOAc 4:1). Remove the solvent under vacuum. Dissolve the residue in EtOAc and wash with water. Dry and concentrate the organic layer. Use the crude material without further purification. Add 4-

- (trifluoromethyl)benzonitrile (2.0 mol) and potassium *tert*-butoxide (0.6 mmol) to a solution of acylhydrazine a compound of formula **B** of scheme 2 (1.0 mmol) in MeOH (2.4 M). Stir the mixture at reflux 24 h. Follow the reaction by TLC (Hexane/EtOAc 4:1). Quench the crude material with water, remove the MeOH in vacuo and extract the aqueous layer with EtOAc. Separate the organic layer, dry with MgSO₄, and concentrate in vacuum. Purify the crude material by Biotage (Hexane/EtOAc 4:1) to obtain a compound of formula **C** of scheme 2 as a white solid.



R = alkyl group

- Triazole alkylation: Add powdered KOH (2.2 mmol), R-I (Br) (2.0 mmol) and Bu₄NBr (0.2 mmol) to a solution of the corresponding triazole derivate compound **C** of scheme 2 (1.0 mmol) in THF (5 mL/mmol). Stir the mixture at room temperature overnight. Follow the reaction by TLC (Hexane/EtOAc 4:1). Quench the crude with water and add EtOAc. Extract the aqueous layer with EtOAc (2X). Separate the organic layer, dry with MgSO₄, and concentrate in vacuum. Purify the crude material by Biotage (Hexane/EtOAc 7:1 and 4:1) to obtain a compound of formula **D** of scheme 2.

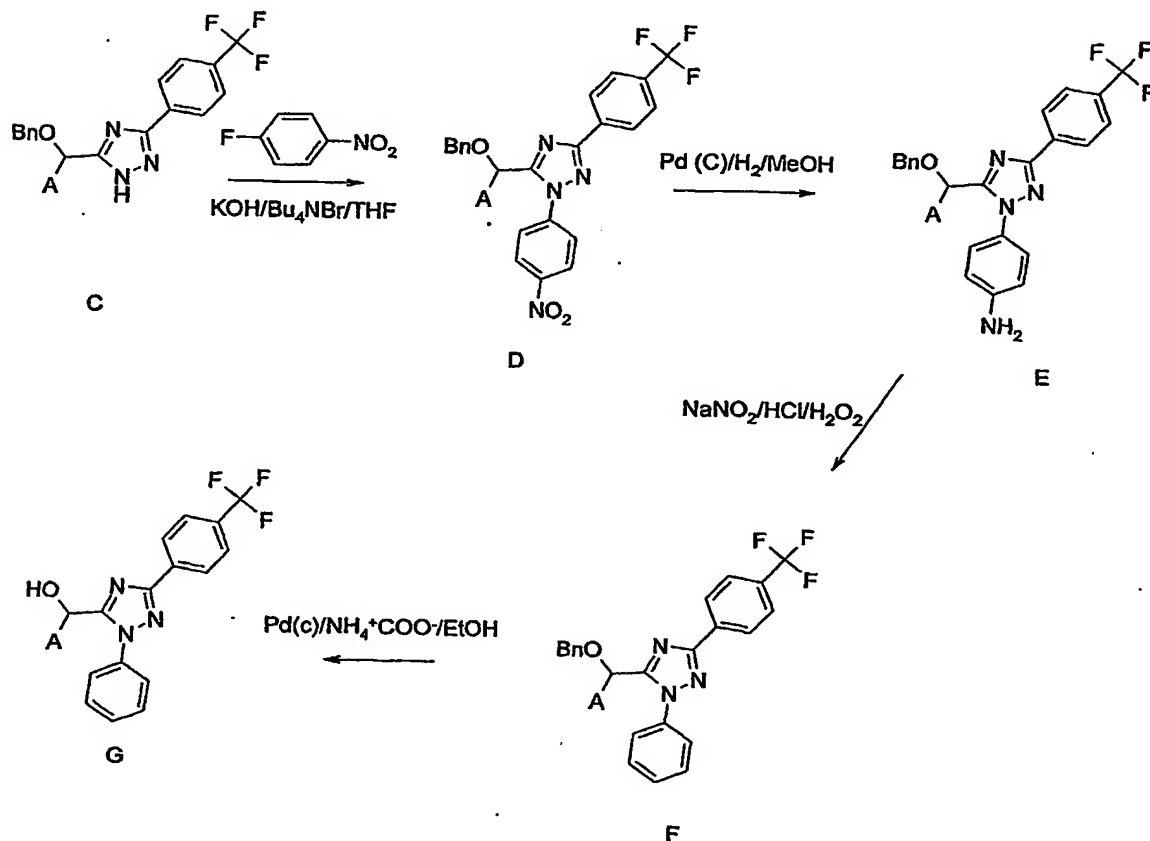


- Add Pd (C) (10-20% in weight) and NH₄⁺COO⁻ (10-20 mmol) to a solution of triazole compound of formula **D** of scheme 2 (1.0 mmol) in EtOH (5 mL/mmol). Stir the mixture at 80°C overnight. Follow the reaction by TLC. Filter the reaction through celite

and remove the solvent under vacuum. Purify the crude material by Biotage (Hexane/EtOAc 1:1) to obtain a compound of formula E of scheme 2.

SCHEME 2A

5



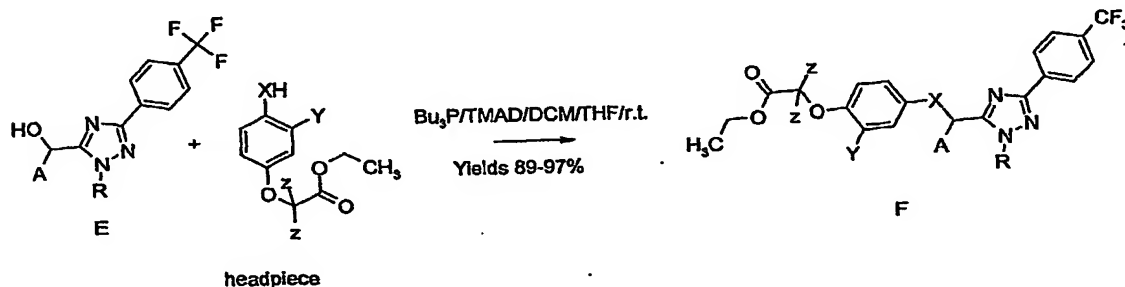
Add K₂CO₃ (1.1 mmol) and 4-fluoro-nitrobenzene (1.0 mmol) to a solution of the corresponding triazole derivate (C) of scheme 2a (1.0 mmol) in DMSO (20 mL/mmol) and stir the mixture to 90°C overnight. Follow the reaction by TLC (Hexane/EtOAc 4:1). Quench the reaction with ice/water and add DCM. Extract again with 20% DCM/MeOH. Combine the organic layers and dry with MgSO₄, and concentrate in vacuum. Purify the crude by flash chromatography (Hexane/EtOAc 9:1) to obtain formula D of scheme 2a.

Add Pd (C) (10% in weight) to a solution of the triazole derivate formula D of scheme 2a (1.0 mmol) in EtOH (5 mL/mmol). Stir the mixture with and in an atmosphere of hydrogen overnight. Follow the reaction by TLC. Filter the solution mixture through

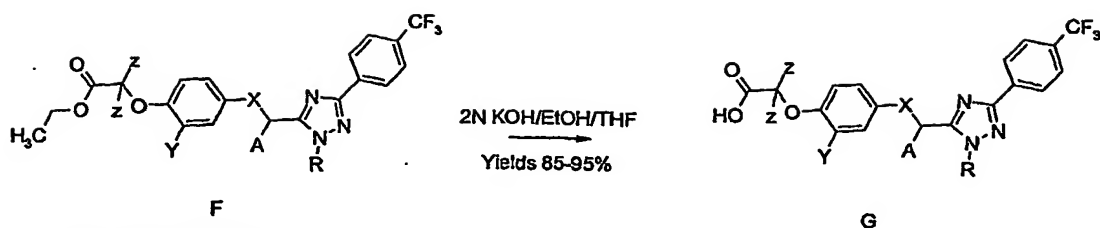
celite and then remove the solvent under vacuum. Purify the crude (formula E of scheme 2a) without further purification.

5 Add 2N HCl solution (10.0 mmol) to a solution of the corresponding triazole derivative formula E of scheme 2a (1.0 mmol) in a mixture solvent (THF/CH₃COOH 8:1) (8 mL/mmol) at 0°C and stir the mixture for 5 minutes at this temperature. Then, add NaNO₂ (1.0 mmol) in water (0.32 M) and then 3% H₂O₂ solution. Stir the reaction at 0°C for 30 minutes and then for 1 hour at room temperature. Then, add EtOAc and extract the mixture with water. Dry the organic layers with MgSO₄ and concentrate in vacuum. Purify the crude by Biotage (Hexane/EtOAc 9:1) to obtain compound of formula F of
10 scheme 2a (Yield 17%).

Add Pd (C) (10-20% in weight) and NH₄⁺COO⁻ (10-20 mmol) to a solution of a compound of formula F of scheme 2a (1.0 mmol) in EtOH (5 mL/mmol). Stir the mixture at 80°C overnight. Follow the reaction by TLC. Filter the reaction through celite and remove the solvent under vacuum. Purify the crude by Biotage (Hexane/EtOAc 1:1) to
15 obtain compound F of scheme 2a.



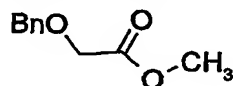
Mitsunobu reaction: Add the head piece (2 mmol), Bu₃P (2.0 mmol) and TMAD
20 (2.0 mmol) to a solution of triazole derivative compound E of scheme 2 (1.0 mmol) in THF/DCM mixture (1:1) (10 mL/mmol). Stir the mixture at room temperature for 10-20 min. Follow the reaction by TLC. Remove the solvent under vacuum and then, add water and diethyl ether. Separate the organic layer and stir with a 2N NaOH solution for 10 min. Extract the mixture, dry the organic layer with MgSO₄, and concentrate in
25 vacuum. Purify the crude by Biotage (Hexane/EtOAc 9:1) to obtain compound F of scheme 2.



Add 2N KOH solution (10 mmol) to a solution of triazole derivate compound F of scheme 2 (1.0 mmol) in EtOH/THF mixture (1:1) (10 mL/mmol) and stir the mixture at room temperature overnight. Follow the reaction by TLC. Remove the solvent under vacuum and then, add water and EtOAc. Add 1N HCl solution until the pH is 5-7. Extract the mixture, wash the organic layer with water, separate, dry with MgSO₄, and concentrate in vacuum. Obtain the compound G of scheme 2 as a white solid.

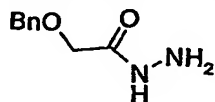
Synthesis of Example 13

PREPARATION 2



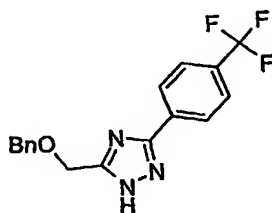
Add BnBr (72.7 mL, 0.61 mol, 1.1 eq) and Ag₂O (141.6 g, 0.61 mol, 1.1 eq) to a solution of methyl glycolate (50 g, 0.56 mol) in EtOAc (300 mL) and stir the mixture to reflux overnight. Follow the reaction by TLC (Hexane /EtOAc 1:1). Filter the reaction through celite and remove the solvent under vacuum. The oil is passed adsorbed onto flash silica. Place on top of a pad of flash silica (500g) and elute with 20% ethyl acetate/hexane to give 75.8 g (75% yield) of a colorless oil.

PREPARATION 3



Dissolve preparation 2 (7.5 g, 41.6 mmol) in EtOH (100 mL). Then, add hydrazine monohydrate (6.05 mL, 124.9 mmol) and stir the mixture at room temperature overnight. Follow the reaction is by TLC (hexane/EtOAc 4:1). Remove the solvent under vacuum and dissolve the residue in EtOAc and wash with water. Dry the organic layer and concentrate and use the crude without further purification.

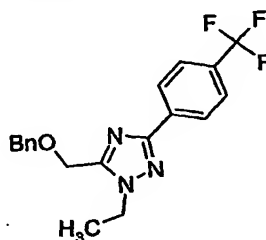
PREPARATION 4



5 Add 4-(trifluoromethyl)benzonitrile (14.2 g, 83.2 mmol) and potassium *tert*-butoxide (2.8 g, 25 mmol) to a solution of preparation 3 in MeOH (100 mL) and stir mixture is at reflux for 24 h. Follow the reaction by TLC (Hexane/EtOAc 4:1). Quench the crude with water, remove the MeOH in vacuum, and extract the aqueous layer with EtOAc. Separate the organic layer, dry with MgSO₄, and concentrate in vacuum. Purify the crude by flash chromatography (Hexane/EtOAc 4:1) to obtain 11.2 g (81% yield) of preparation 4 as a white solid.

10

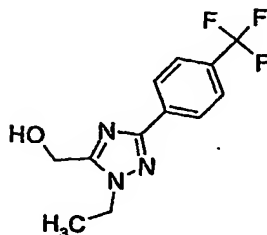
PREPARATION 5



15 Add powdered KOH (0.37 g, 6.6 mmol), EtI (0.48 mL, 6.0 mmol) and Bu₄NBr (0.19 g, 0.6 mmol) to a solution of preparation 4 (1.0 g, 3.0 mmol) in THF (15 mL), and stir the mixture at room temperature overnight. Follow the reaction by TLC (hexane/EtOAc 4:1). Quench the crude with water and add EtOAc. Extract the aqueous layer with EtOAc (2x). Separate the organic layer, dry with MgSO₄, and concentrate in vacuo. Purify the crude by flash chromatography (Hexane/EtOAc 9:1) to obtain 1.09 g (99% yield) of preparation 5 as a white solid.

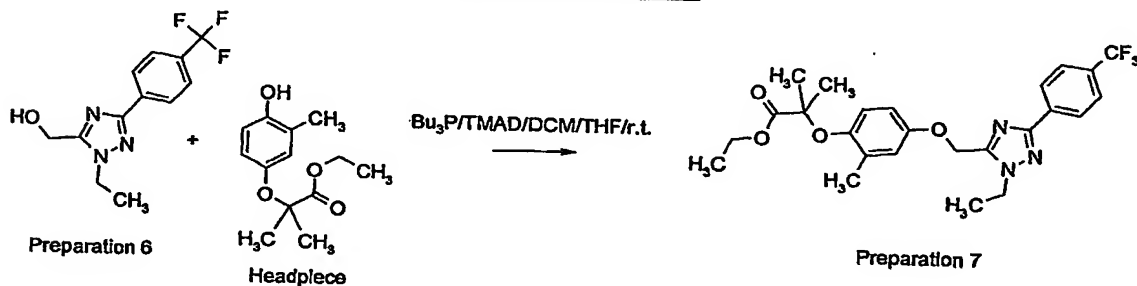
20

PREPARATION 6



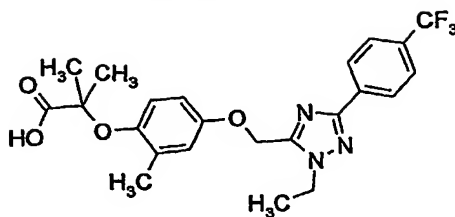
Add Pd (C) (20% in weight) and $\text{NH}_4^+\text{COO}^-$ (1.83 g, 10.0 mmol) to a solution of preparation 5 (1.05 g, 2.9 mmol) in EtOH (25 mL) and stir the mixture at 80°C for 6 hours. Follow the reaction by TLC (Hexane/EtOAc 4:1). Filter the reaction through celite and remove the solvent under vacuum to obtain 0.88 g of preparation 6 as a white solid that is used without further purification.

PREPARATION 7



Add the headpiece (1.38 g, 5.8 mmol), Bu_3P (1.44 mL, 5.8 mmol) and TMAD (0.99 g, 5.8 mmol) to a solution of preparation 6 (0.88 g, 2.9 mmol) in THF/DCM mixture (1:1) (15 + 15 mL) and stir the mixture at room temperature for 1 h. Follow the reaction by TLC (Hexane/EtOAc 1:1). Remove the solvent under vacuum. Then, add water and diethyl ether. Separate the organic layer, and stir with 2N NaOH solution for 10 min. Extract the mixture and dry the organic layer with MgSO_4 , and concentrate in vacuo. Purify the crude by Biotage [40 + S] (Hexane/EtOAc 9:1) to obtain 0.99 g (70% yield) of preparation 7 as a white solid. MS Data (ES^+) m/z 492.3 [$\text{M} + \text{H}$]. 350 mg (fraction B) of impure compound were reserved.

EXAMPLE 13

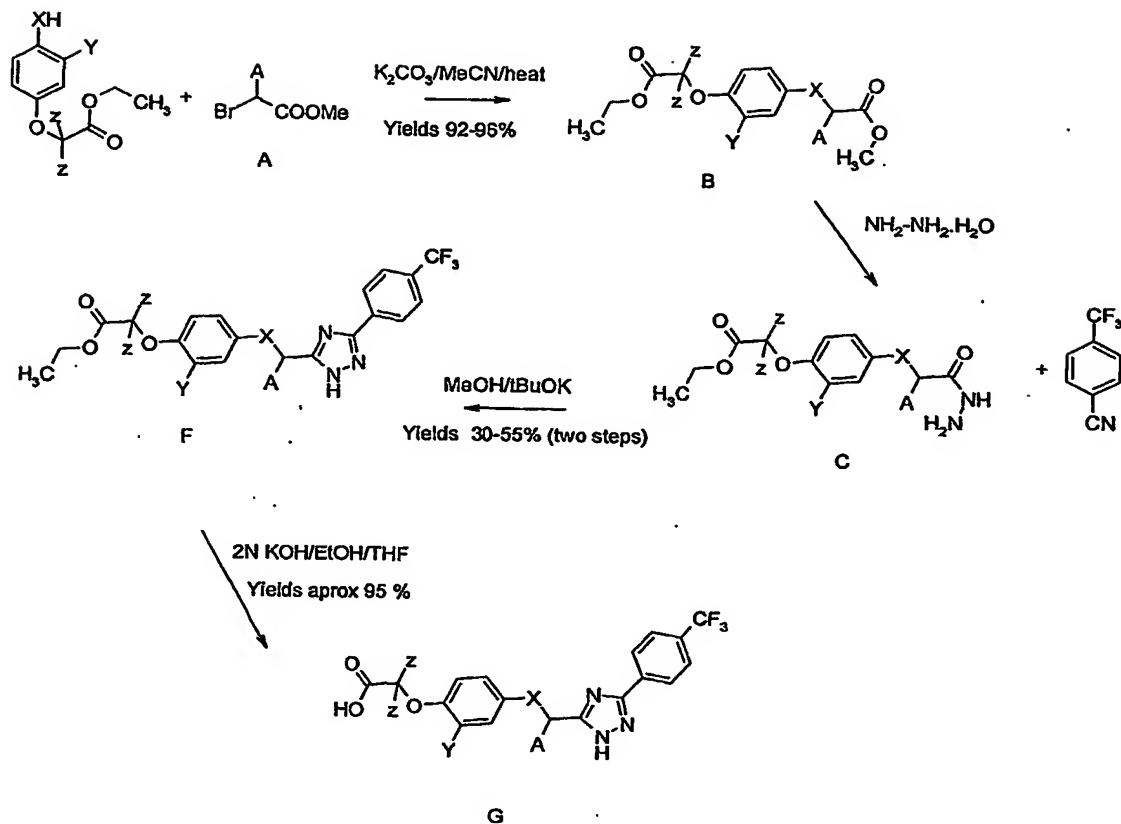


5 Add 2N KOH solution (10 mL, 19.9 mmol) to a solution example XX (0.98 g, 1.99 mmol) in EtOH/THF mixture (1:1) (10 + 10 mL), and stir the mixture at room temperature overnight. Follow the reaction by TLC (Hexane/EtOAc 1:1). Remove the solvent under vacuum. Then, add water and Et₂O and stir the mixture for 2 min. Isolate the organic layer and add 1N HCl solution over aqueous phase until pH 5-7. Filter the white solid precipitate and wash with water. Dry under vacuum to obtain 0.80 g (87% yield) of Example XX (Purity 97%). MS Data (ES⁺) m/z 464.2 [M + H].

10

Examples 12-34 are prepared by a similar procedure for the preparation of example 13.

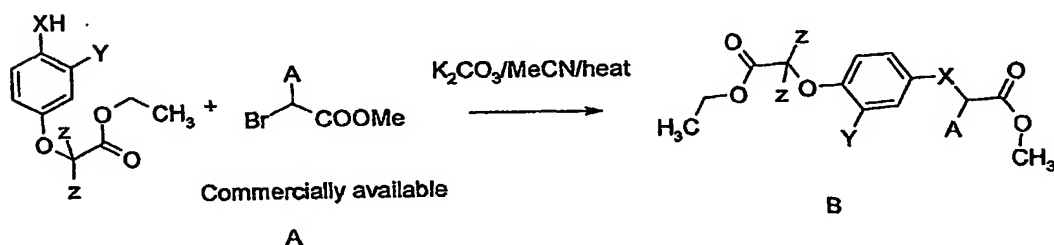
SCHEME 3



Example	Structure	LC/MS [M + 1]
35		436.1
36		421.1

Example	Structure	LC/MS [M + 1]
37		450.2
38		436.1

GENERAL PROCEDURE FOR SCHEME 3

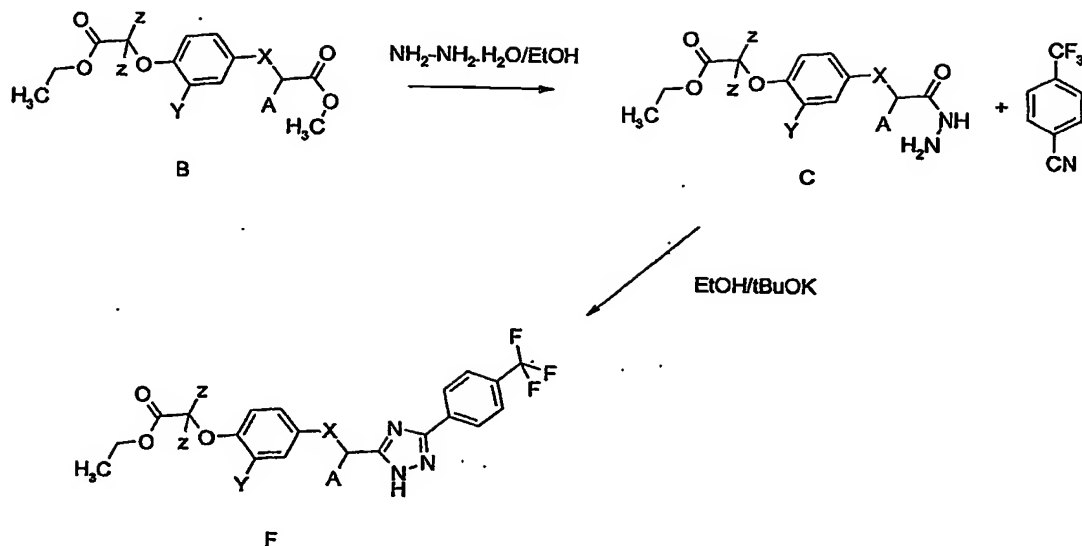


5

Add K_2CO_3 (3.0 mmol) and compound of formula A of scheme 3 (1.0 mmol) to a solution of the bromoester derivate (compound of formula H of scheme 3) (1.2 mmol) in MeCN (5 mL/mmol). Stir the mixture at reflux overnight. Follow the reaction by TLC (Hexane/EtOAc 4:1). Remove the solvent under vacuum and then, add water and EtOAc.

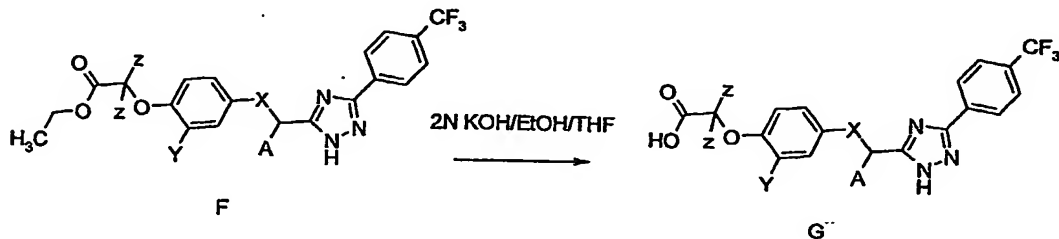
10

Extract the mixture, dry the organic layer with $MgSO_4$, and concentrate in vacuum. Purify the crude by flash chromatography (Hexane/EtOAc 6:1) to obtain compound B of scheme 3 as a colorless oil.



Dissolve ester compound of formula B of scheme 3 (1.0 mmol) in EtOH (0.8 M). Then, add hydrazine monohydrate (3.0 mmol). Stir the mixture at room temperature overnight. Follow the reaction by TLC (hexane/EtOAc 4:1). Remove the solvent under vacuum. Dissolve the residue in EtOAc and wash with water. Dry the organic layer and concentrate. Use the crude without further purification. Add 4-(trifluoromethyl)benzonitrile (2.0 mol) and potassium *tert*-butoxide (0.6 mmol) to a solution of acylhydrazine compound of formula C of scheme 3 (1.0 mmol) in EtOH (2.4 M). Stir the mixture at reflux 24 hours. Follow the reaction by TLC (hexane/EtOAc 4:1). Quench the crude with water, remove the MeOH in vacuo, and extract the aqueous layer with EtOAc. Separate the organic layer, dry with MgSO₄, and concentrate in vacuum. Purify the crude by Biotage (Hexane/EtOAc 6:1) to obtain the compound of formula F of scheme 3 as a colorless oil.

15

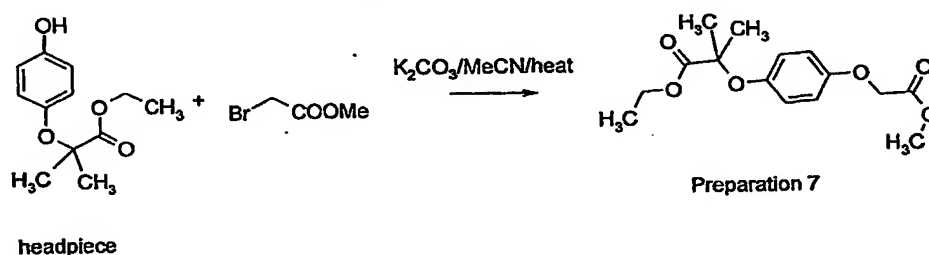


- Add 2N KOH solution (10 mmol) to a solution of triazole derivate compound of formula F of scheme 3 (1.0 mmol) in EtOH/THF mixture (1:1) (10 mL/mmol). Stir the mixture at room temperature overnight. Follow the reaction by TLC. Remove the solvent under vacuum. Then, add water and EtOAc. Add 1N HCl solution until pH 5-7.
- 5 Extract the mixture, wash the organic layer with water, separate, dry with MgSO_4 , and concentrate in vacuum. Obtain the products of the compound of formula G of scheme 3 as white solids.

SYNTHESIS OF EXAMPLE 36

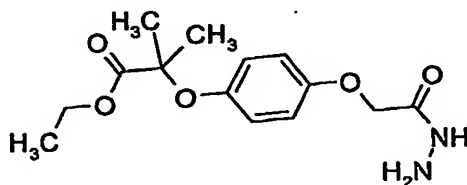
10

PREPARATION 8



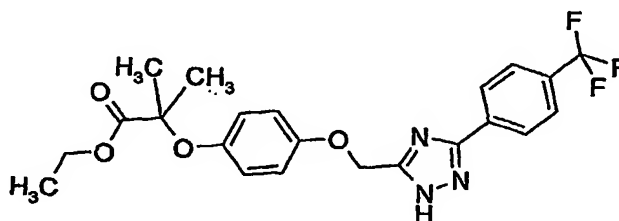
- Add K_2CO_3 (9.23 g, 66.9 mmol) and headpiece (5.0 g, 22.3 mmol) to a solution of
- 15 commercially available bromoester derivate (2.54 mL, 26.8 mmol) in MeCN (100 mL) and stir the mixture at reflux overnight. Follow the reaction by TLC (Hexane/EtOAc 4:1). Remove the solvent under vacuum. Then, add water and EtOAc. Extract the mixture and dry the organic layer with MgSO_4 and concentrate in vacuum. Purify the crude by flash chromatography (Hexane/EtOAc 19:1) to obtain preparation 8 as a
- 20 colorless oil (6.59 g).

PREPARATION 9



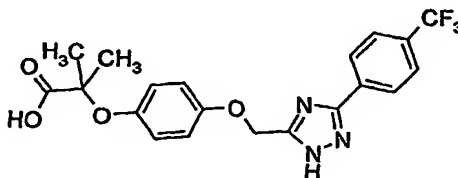
Dissolve preparation 8 (6.59 g, 22.3 mmol) in EtOH (30 mL). Then, add hydrazine monohydrate (4.32 mL, 89.2 mmol) and stir the mixture at room temperature overnight. Follow the reaction by TLC (hexane/EtOAc 4:1). Remove the solvent under vacuum. Dissolve the residue in EtOAc and wash with water. Dry the organic layer and concentrate. Use the crude preparation 9 without further purification.

PREPARATION 10



Add 4-(trifluoromethyl)benzonitrile (4.72 g, 27.6 mmol) and potassium *tert*-butoxide (0.93 g, 8.3 mmol) to a solution of acylhydrazine preparation 9 (3.22 g, 10.9 mmol) in EtOH (50 mL) and stir the mixture at reflux 24 h. Follow the reaction by TLC (Hexane/EtOAc 4:1). Quench the crude with water, remove the MeOH in vacuo and extract the aqueous layer with EtOAc. Separate the organic layer, dry with MgSO₄, and concentrate in vacuum. Purify the crude by Biotage (Hexane/EtOAc 9:1 to 6:1) obtain preparation 10 as a white solid (2.28 g obtained, 47% yield two steps).

EXAMPLE 36

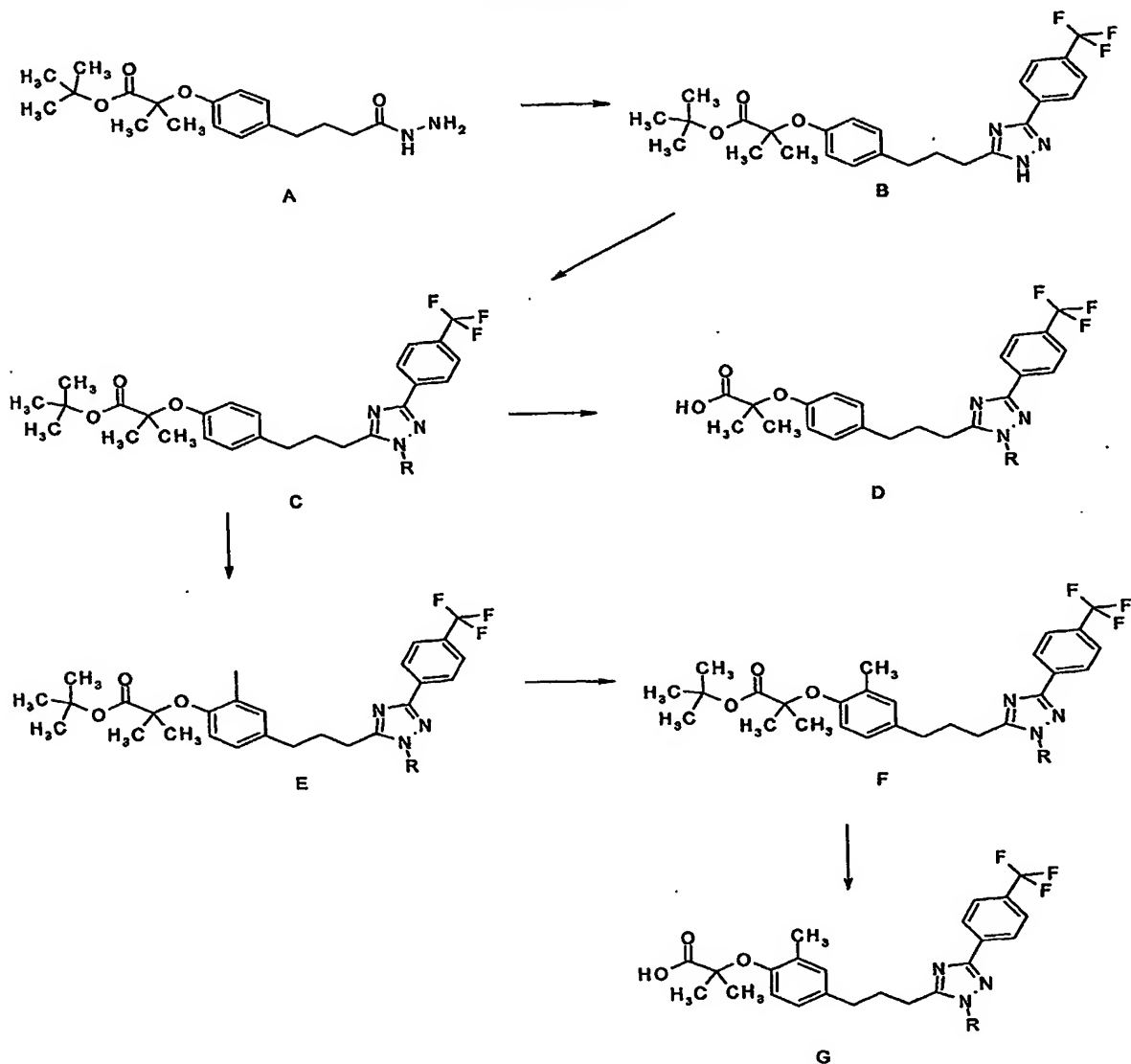


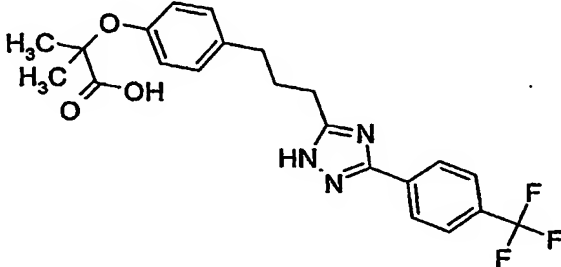
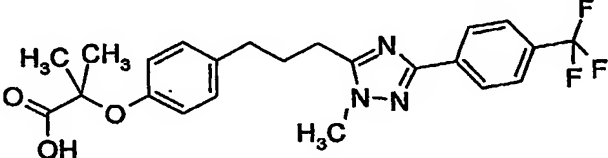
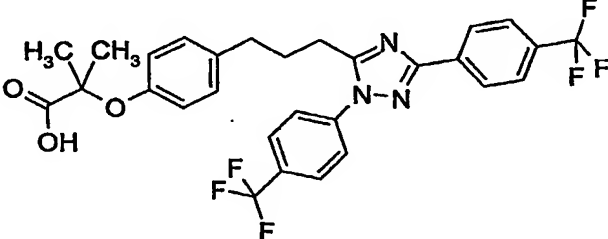
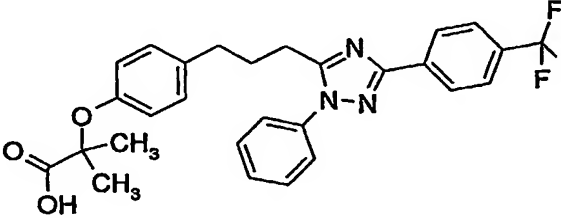
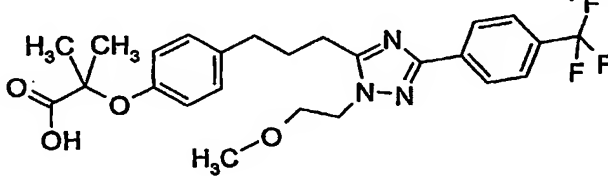
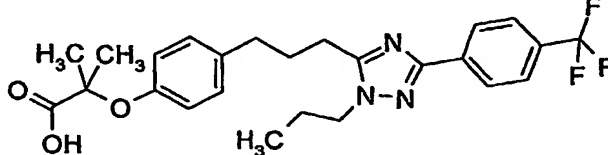
Add 2N KOH solution (2.7 mL, 4.5 mmol) to a solution of preparation 10 (200 mg, 0.45 mmol) in EtOH/THF mixture (1:1) (8 mL) and stir the mixture at room temperature overnight. Follow the reaction by TLC. Remove the solvent under vacuum. Then, add water and EtOAc. Add 1N HCl solution until pH 5-7. Extract the mixture and wash the organic layer with water, separate, dry with MgSO₄, and concentrate in vacuum. Obtain example 36 as white solids (164 mg, 87% yield).

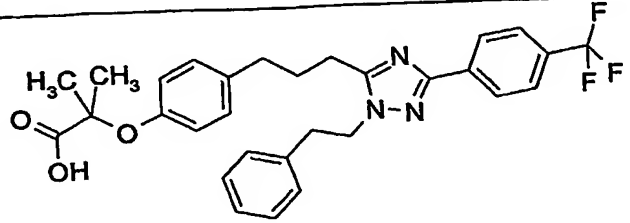
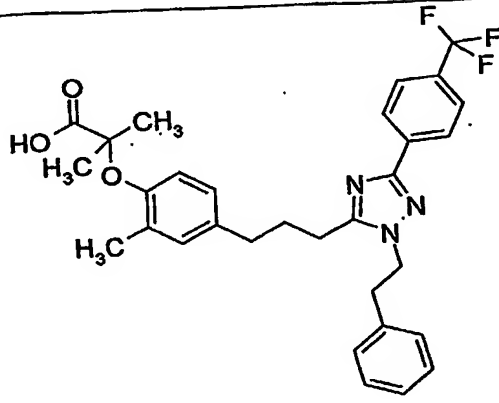
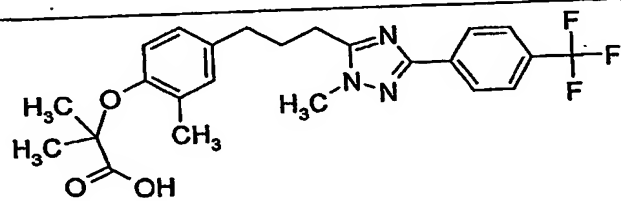
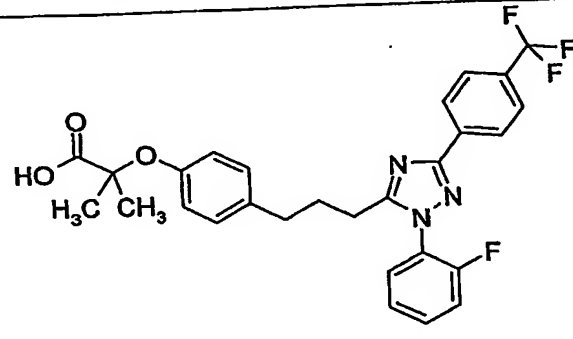
Examples 35, 37 and 38 are prepared by a similar procedure for the preparation of example 36.

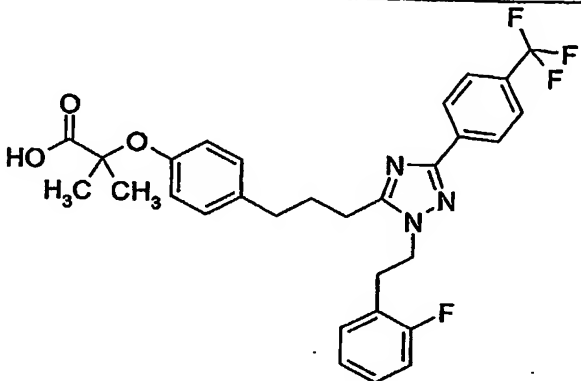
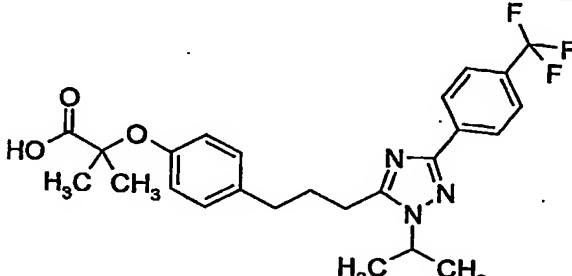
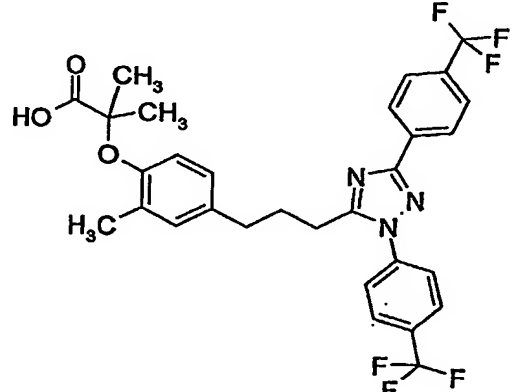
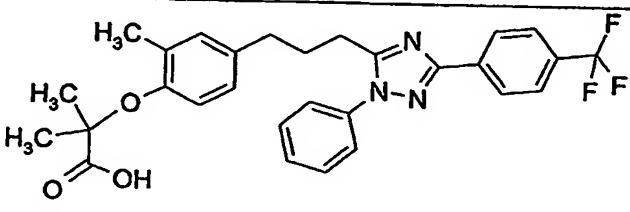
5

SCHEME 4

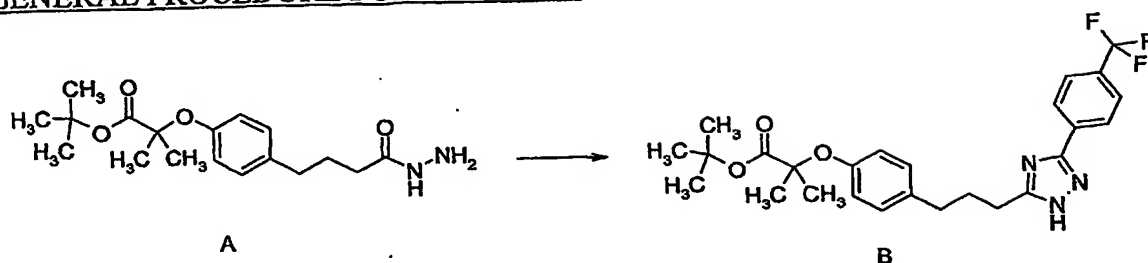


Example	Structure	LC/MS [M + 1]
39		434.3
40		448.1
41		578.2
42		Only 1H-NMR
43		492.0
44		Only 1H-NMR

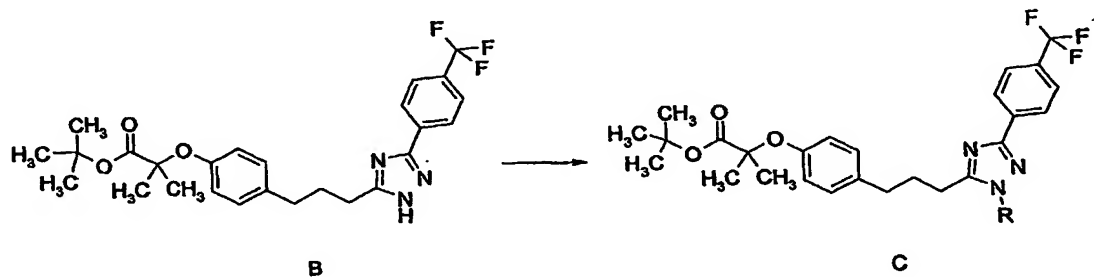
Example	Structure	LC/MS [M + 1]
45		Only 1H-NMR
46		552.5
47		528.3
48		528.3

Example	Structure	LC/MS [M + 1]
49		556.2
50		476.2
51		592.3
52		524.2

GENERAL PROCEDURE FOR SCHEME 4



- Add 4-(trifluoromethyl)benzonitrile (3.0 mol) and potassium *tert*-butoxide (0.21 mmol) to a solution of a compound of formula A of scheme 4 (1.5 mmol) in MeOH (5 mL) and stir the mixture at reflux overnight. Add an additional 0.2 equivalents of potassium *tert*-butoxide and stir the reaction for 24 hours. Quench the crude with water, remove the MeOH in vacuo, and extract the aqueous layer with EtOAc. Separate the organic layer, dry with MgSO₄, and concentrate in vacuum. Purify the crude by Biotage (Hexane/EtOAc 4:1) yielding a compound of formula B of scheme 4 as a pale yellow oil.
- MS Data (ES⁺) m/z 490.6 [M + H]



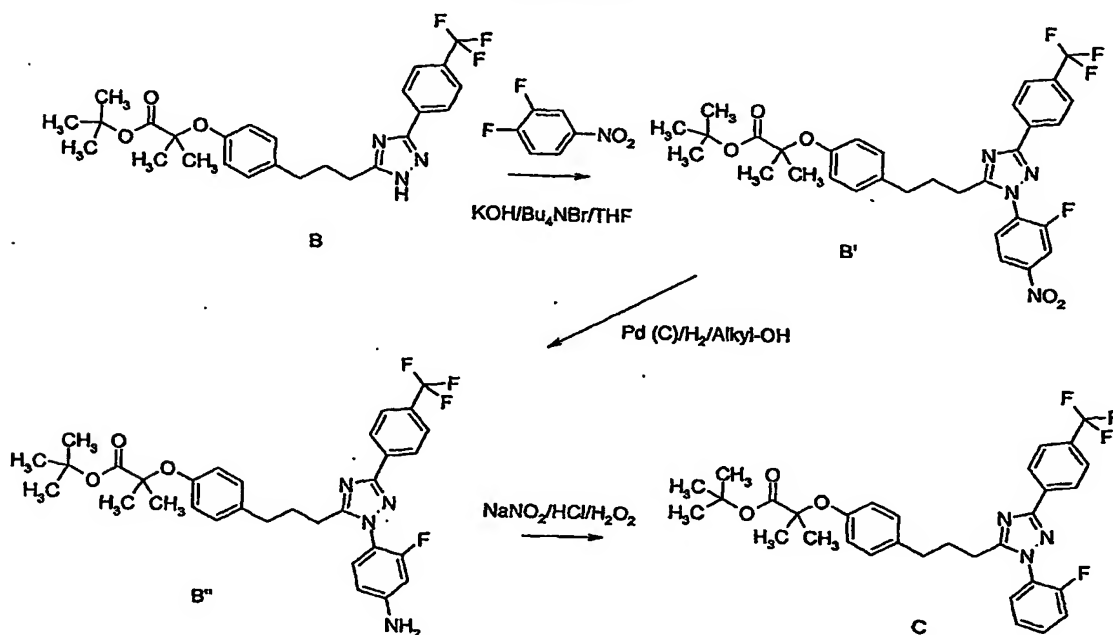
R = Alkyl group

- Triazole alkylation:** Add powdered KOH (2.2 mmol), R-I (Br) (2.0 mmol) and Bu₄NBr (0.2 mmol) to a solution of the corresponding triazole compound of formula B of scheme 4 (1.0 mmol) in THF (5 mL/mmol) and stir the mixture at room temperature overnight. Follow the reaction by TLC (hexane/EtOAc 4:1). Quench the crude with water and add EtOAc. Extract the aqueous layer with EtOAc (2x). Separate the organic layer, dry with MgSO₄, and concentrate in vacuum. Purify the crude by Biotage (Hexane/EtOAc 7:1 and 4:1) to obtain a compound of formula C of scheme 4 as a white solid.

R = Aryl group (Ph and *p*-CF₃-Ph)

10

Scheme 4a



R = Aryl group (*o*-F-Ph)

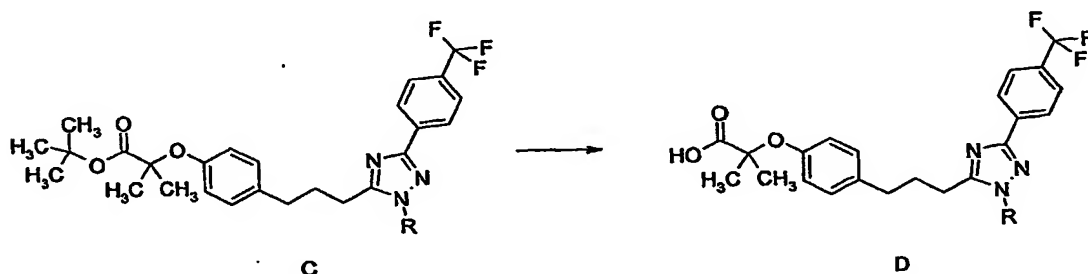
15 Add K_2CO_3 (1.1 mmol) and 3,4-difluoro-nitrobenzene (1.0 mmol) to a solution of the corresponding triazole compound of formula **B** (1.0 mmol) in DMSO (20 mL/mmol) and stir the mixture to 90°C overnight. Follow the reaction by TLC (Hexane/EtOAc 4:1). Quench the crude with ice/water and add DCM. Extract a second extraction with 20% DCM/MeOH. Combine the organic layers, dry with $MgSO_4$, and concentrate in vacuum.

Purify the crude by flash chromatography (Hexane/EtOAc 9:1) to obtain a compound of formula B' of scheme 4a.

Add Pd (C) (10% in weight) to a solution of triazole derivate (1.0 mmol) in alcohol (5 mL/mmol). Stir the mixture with and in an atmosphere of hydrogen overnight.

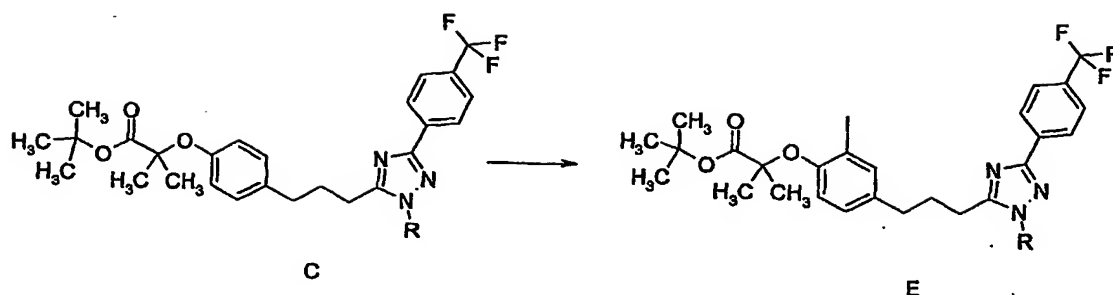
- 5 Follow the reaction by TLC. Filter the solution mixture through celite and remove the solvent under vacuum and use the crude without further purification.

- 10 Add 2N HCl solution (10.0 mmol) to a solution of the corresponding triazole compound B'' of scheme 4a (1.0 mmol) in a mixture solvent (THF/CH₃COOH 8:1) (8 mL/mmol) at 0°C. Stir the mixture 5 minutes at this temperature and add NaNO₂ (1.0 mmol) in water (0.32 M) and then 3% H₂O₂ solution (0.56 mL). Stir the reaction at 0°C for 30 min and 1 hour at room temperature. Then, add EtOAc and extract the mixture with water. Dry the organic layer with MgSO₄ and concentrate in vacuum. Purify the crude by Biotage (Hexane/EtOAc 9:1) to obtain compound C' of scheme 4a (Yield 17%).

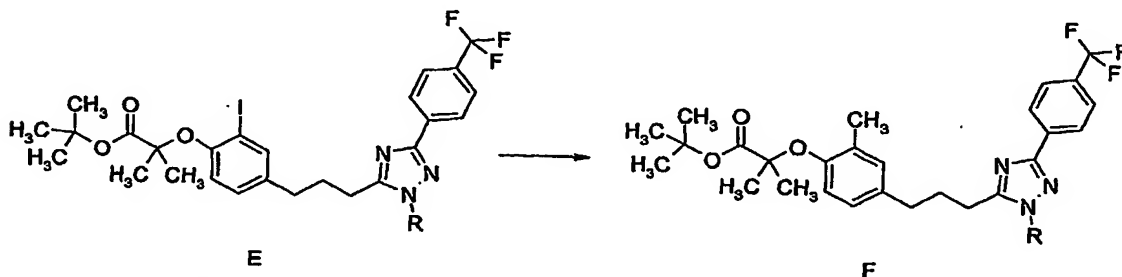


15

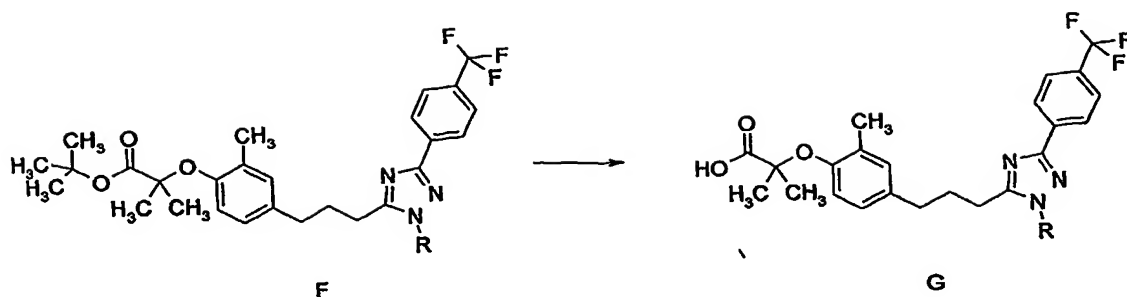
- Add TFA (excess) to a solution of compound of formula C of scheme 4 (1.0 mmol) in CH₂Cl₂ (5 ml) and stir the mixture at room temperature overnight. Follow the reaction by TLC (Hexane/EtOAc 1:1). Remove the solvent and residual TFA in vacuum.
- 20 Dissolve the residue in DCM and wash with a saturated solution of NaHCO₃. Dry the organic layer with MgSO₄ and concentrate in vacuum. Obtain the compound of formula D of scheme 4 as a solid.



Add I₂ (2.0 mmol) and AgSO₄ (2.0 mmol) to a solution of the corresponding triazole compound of formula **D** of scheme 4 (1.0 mmol) in EtOH (8 mL/mmol) and stir the mixture at room temperature overnight. Follow the reaction by TLC (Hexane/EtOAc 4:1). Quench the crude with water and add EtOAc. Extract the aqueous layer with EtOAc (2x). Separate the organic layer, dry with MgSO₄, and concentrate in vacuum. Purify the crude by Biotage (Hexane/EtOAc 7:1 and 4:1) to obtain a compound of formula **E** of scheme 4 as a white solid.



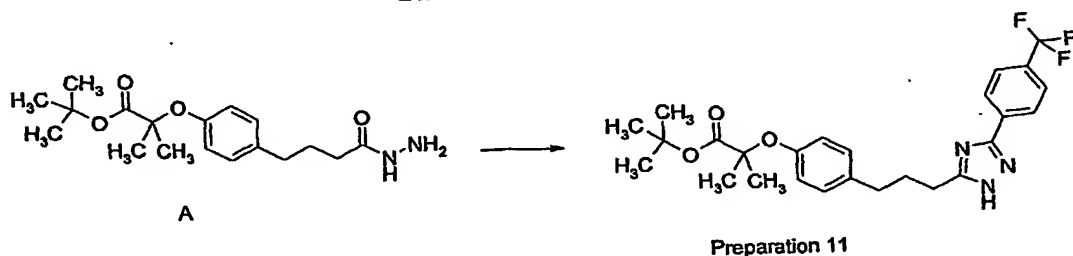
Add MeB(OH)_2 (3.0 mmol), CsF (3.0 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.16 mmol) to a solution of the corresponding triazole compound of formula E of scheme 4 (1.0 mmol) in anhydrous Dioxane (10 mL/mmol) under N_2 . Stir the mixture to 80°C overnight. Follow the reaction by LC/MS. Cool the reaction, filter through celite, and remove the solvent under vacuum. Purify the crude by flash chromatography (Hexane/EtOAc 7:1 and 4:1 mixtures) to obtain a compound formula F of scheme 4 as a white solid.



Add TFA (excess) to a solution of a compound of formula F of scheme 4 (1.0 mmol) in CH_2Cl_2 (5 ml) and stir the mixture at room temperature overnight. Follow the reaction by TLC (Hexane/EtOAc 1:1). Remove the solvent and residual TFA in vacuum. Dissolve the residue in DCM and wash with saturated solution of NaHCO_3 . Dry the organic layer with MgSO_4 and concentrate in vacuum. Obtain a compound of formula G of scheme 4 as a pure solid.

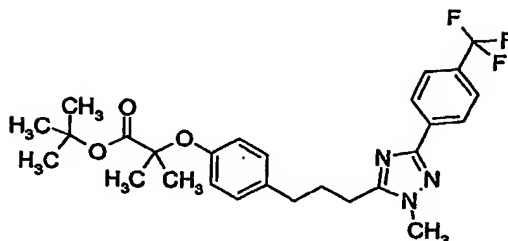
10 SYNTHESIS OF EXAMPLE 47

PREPARATION 11



Add 4-(trifluoromethyl)benzonitrile (0.51 g, 3.0 mol) and potassium *tert*-butoxide (0.023 g, 0.21 mmol) to a solution of A above (0.5 g, 1.5 mmol) in MeOH (5 mL) and stir the mixture at reflux overnight. Add an additional 0.2 equivalents of potassium *tert*-butoxide and stir the reaction for 24 h. Quench the crude with water, remove the MeOH in vacuo and extract the aqueous layer with EtOAc. Separate the organic layer, dry with MgSO_4 , and concentrate in vacuo. Purify the crude by Biotage (Hexane/EtOAc 4:1) yielding 0.32 g (44 %) preparation 11 as a pale yellow oil. MS Data (ES^+) m/z 490.6 [$\text{M} + \text{H}$].

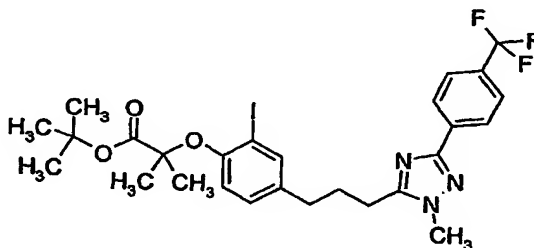
PREPARATION 12



Add powdered KOH (0.14 g, 2.45 mmol), MeI (0.14 mL, 2.3 mmol) and Bu₄NBr (0.05 g, 0.15 mmol) to a solution of preparation 11 (0.75 g, 1.5 mmol) in THF (5 mL) and stir the mixture at room temperature overnight. Follow the reaction by TLC (hexane/EtOAc 4:1). Quench the crude with water and add EtOAc. Extract the aqueous layer with EtOAc (2x). Separate the organic layer, dry with MgSO₄, and concentrate in vacuo. Purify the crude by flash chromatography (Hexane/EtOAc 9:1) to obtain 0.51 g (66% yield) of preparation 12 a white solid.

10

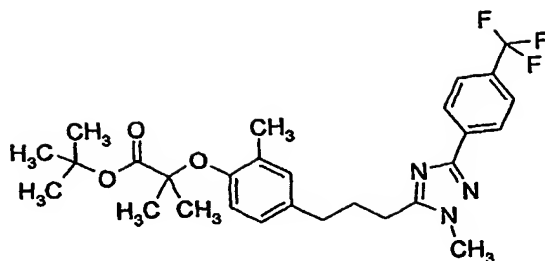
PREPARATION 13



Add I₂ (0.2 g, 0.8 mmol) and AgSO₄ (0.25 g, 0.8 mmol) to a solution of preparation 12 (0.25 g, 0.5 mmol) in EtOH (5 mL) and stir the mixture at room temperature overnight. Follow the reaction by TLC (Hexane/EtOAc 4:1). Quench the crude with water and add EtOAc. Extract the aqueous layer with EtOAc (2x). Separate the organic layer, dry with MgSO₄, and concentrate in vacuum. Purify the crude by Biotage (Hexane/EtOAc 9:1) to obtain 0.15 g (48% yield) of preparation 13 as a white solid.

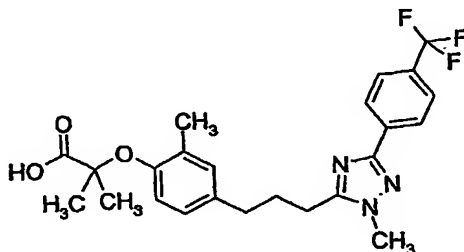
20

PREPARATION 14



Add MeB(OH)₂ (0.04 g, 0.71 mmol), CsF (0.11 g, 0.71 mmol) and PdCl₂(dppf) (0.03 g, 0.04 mmol) to a solution of the preparation 13 (0.15 g, 0.24 mmol) in anhydrous Dioxane (2 mL) under N₂ and stir the mixture to 80°C overnight. Follow the reaction by
5 LC/MS. Cool and then filter the reaction through celite and remove the solvent under vacuum. Purify the crude by flash chromatography (Hexane/EtOAc 4:1 mixtures) to obtain 0.09 g (72% yield) of preparation 14 as a white solid.

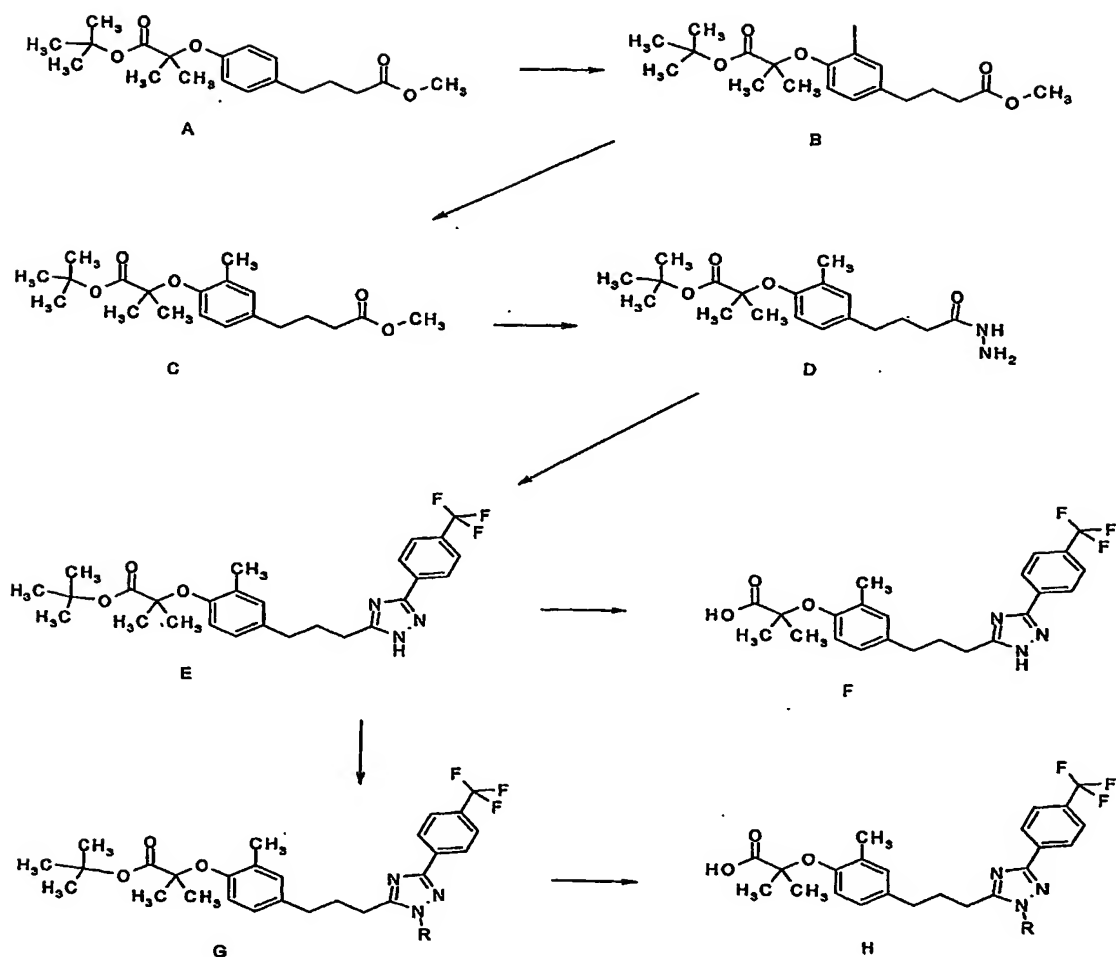
EXAMPLE 47



10 Add TFA (excess) to a solution of preparation 14 (0.09 g, 0.17 mmol) in CH₂Cl₂ (5 ml) and stir the mixture at room temperature overnight. Follow the reaction by TLC (Hexane/EtOAc 4:1). Remove the solvent and residual TFA in vacuum. Dissolve the residue in DCM and wash with saturated solution of NaHCO₃. Dry the organic layer with
15 MgSO₄ and concentrate in vacuum. Obtain example 47 as a solid, 0.05 g (92% yield).

Examples 39-46 and 48-52 are prepared by a similar procedure for the preparation of example 47.

SCHEME 5

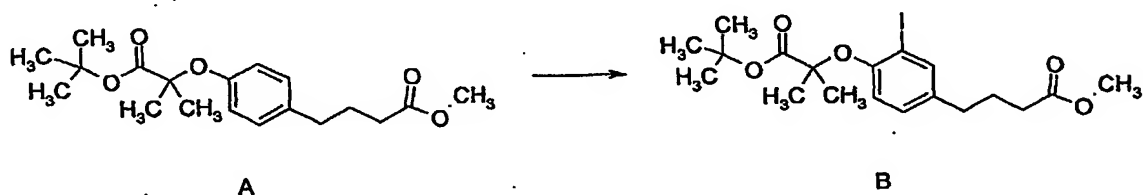


5

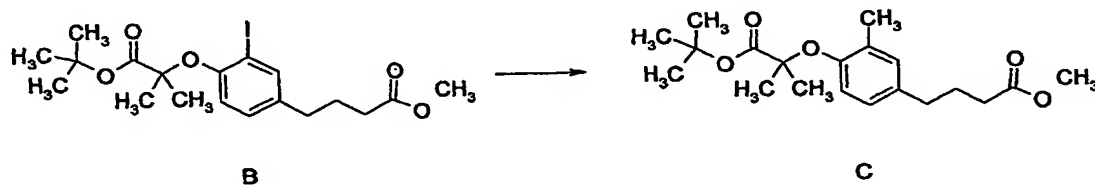
Example	Structure	LC/MS [M + 1]
53		448.4

Example	Structure	LC/MS [M + 1]
54		490.3

GENERAL PROCEDURE FOR SCHEME 5



- 5 Add I₂ (1.1 mmol) and AgSO₄ (1.1 mmol) to a solution of a compound of formula A of scheme 5 (1.0 mmol) in EtOH (8 mL/mmol) and stir the mixture at room temperature overnight. Follow the reaction by TLC (Hexane/EtOAc 4:1). Quench the crude with water and add EtOAc. Extract the aqueous layer with EtOAc (2x). Separate the organic layer, dry with MgSO₄, and concentrate in vacuum. Purify the crude by
- 10 Biotage (Hexane/EtOAc 9:1) to obtain a compound of formula B of scheme 5 (Yield 56%) as a white solid.

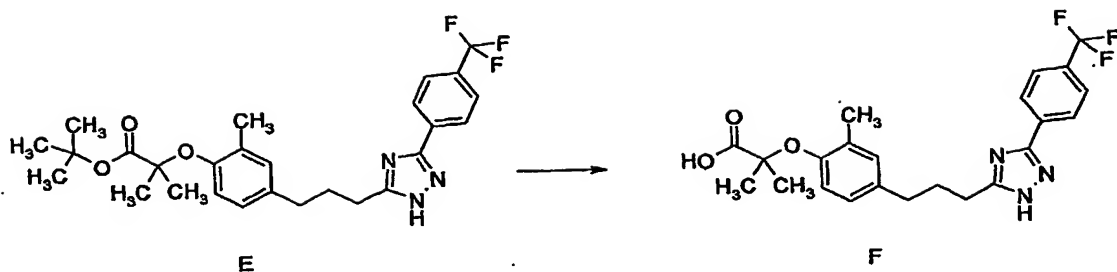


- 15 Add MeB(OH)₂ (3.0 mmol), CsF (3.0 mmol) and PdCl₂(dppf) (0.16 mmol) to a solution of a compound of formula B of scheme 5 (1.0 mmol) in anhydrous Dioxane (10 mL/mmol) under N₂ and stir the mixture to 80°C overnight. Follow the reaction by

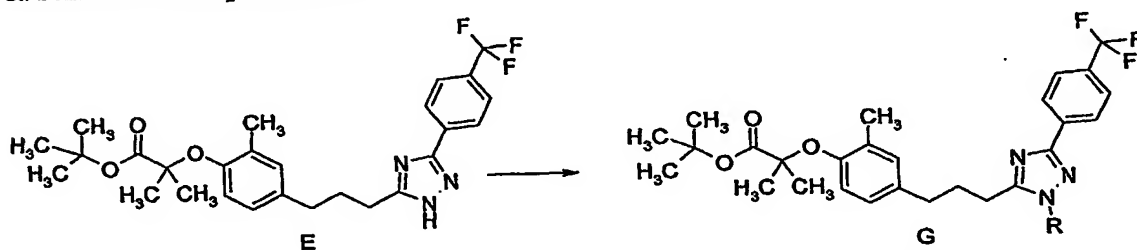
10
.
15



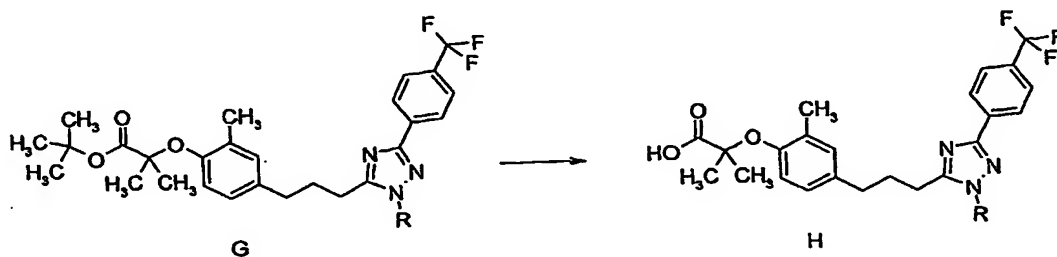
Dissolve the a compound of formula C of scheme 5 (1.0 mmol) in EtOH (0.8 M). Then, add hydrazine monohydrate (3.0 mmol) and stir the mixture at room temperature overnight. Follow the reaction by TLC (hexane/EtOAc 4:1). Remove the solvent under vacuum. Dissolve the residue in EtOAc and wash with water. Dry the organic layer and concentrate and use the crude without further purification. Add 4-(trifluoromethyl)benzonitrile (2.0 mol) and potassium *tert*-butoxide (0.6 mmol) to a solution of acylhydrazine compound of formula D of scheme 5 (1.0 mmol) in MeOH (2.4 M). Stir the mixture at reflux 24 hours. Follow the reaction by TLC (Hexane/EtOAc 4:1). Quench the crude with water, remove the MeOH in vacuo, and extract the aqueous layer with EtOAc. Separate the organic layer, dry with MgSO₄, and concentrate in vacuum. Purify the crude by Biotage (Hexane/EtOAc 4:1 and 2:1) to obtain a compound of formula E of scheme 5 (Yield 22%) as a white solid.



- Add TFA (excess) to a solution of compound of formula E of scheme 5 (1.0 mmol) in CH_2Cl_2 (5 ml) and stir the mixture at room temperature overnight. Follow the reaction by TLC (Hexane/EtOAc 1:1). Remove the solvent and residual TFA in vacuum.
- 5 Dissolve the residue in DCM and wash with a saturated solution of NaHCO_3 . Dry the organic layer with MgSO_4 and concentrate in vacuum. Obtain the compound of formula F of scheme 5 as a pure solid.



- Add powdered KOH (2.2 mmol), R-I (Br) (2.0 mmol) and Bu_4NBr (0.2 mmol) to a solution of the corresponding triazole derivate compound of formula E of scheme 5 (1.0 mmol) in THF (5 mL/mmol) and stir the mixture at room temperature overnight. Follow the reaction by TLC (hexane/EtOAc 4:1). Quench the crude with water and add EtOAc. Extract the aqueous layer with EtOAc (2x), separate the organic layer, dry with MgSO_4 , and concentrate in vacuum. Purify the crude by Biotage (Hexane/EtOAc 7:1 and 4:1) to
- 15 obtain compound of formula G of scheme 5 as a white solid.

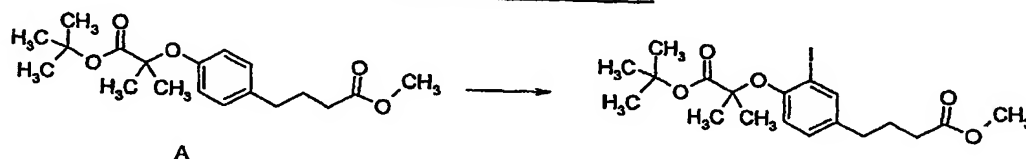


Add TFA (excess) to a solution of compound of formula G of scheme 5 (1.0 mmol) in CH_2Cl_2 (5 ml) and stir the mixture at room temperature overnight. Follow the reaction by TLC (Hexane/EtOAc 1:1). Remove the solvent and residual TFA in vacuum. Dissolve the residue in DCM and wash with a saturated solution of NaHCO_3 . Dry the organic layer with MgSO_4 and concentrate in vacuum. Obtain compound of formula H of scheme 5 as a solid.

SYNTHESIS OF EXAMPLE 54

10

PREPARATION 15

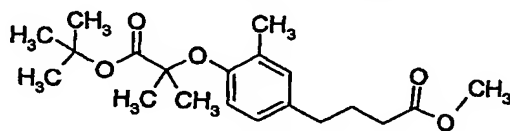


Preparation 15

Add I_2 (18.2 g, 71.4 mmol), and AgSO_4 (22.2 g, 71.4 mmol) to a solution of the corresponding triazole derivate (compound A above) (20 g, 64.4 mmol) in EtOH (65 mL) and stir the mixture at room temperature overnight. Follow the reaction by TLC (Hexane/EtOAc 4:1). Quench the crude with water and add EtOAc. Extract the aqueous layer with EtOAc (2x). Separate the organic layer, dry with MgSO_4 , and concentrate in vacuum. Purify the crude by Biotage (Hexane/EtOAc 9:1) to obtain preparation 15 as a white solid (m= 15.8 g, Yield 56%).

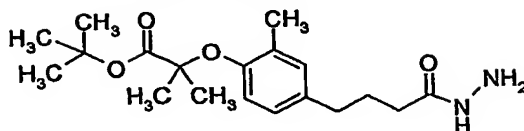
20

PREPARATION 16



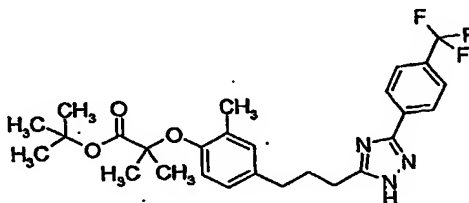
Add MeB(OH)_2 (3.48 g, 58.2 mmol), CsF (13.8 g, 91.0 mmol) and $\text{PdCl}_2(\text{dppf})$ (4.75 g, 5.82 mmol) to a solution of preparation 15 (15.8 g, 36.4 mmol) in anhydrous Dioxane (40 mL) under N_2 and stir the mixture to 80°C overnight. Follow the reaction by LC/MS. Cool and then filter the reaction through celite and remove the solvent under vacuum. Purify the crude by flash chromatography (Hexane/EtOAc 19:1 mixtures) to obtain 7.75 g (66% yield) of preparation 16 as a white solid.

PREPARATION 17



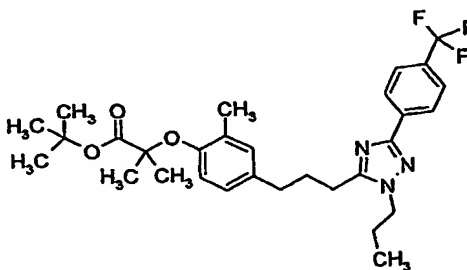
5 Dissolve preparation 16 (7.75 g, 24.04 mmol) in EtOH (50 mL). Then, add hydrazine monohydrate (4.66 mL, 96.2 mmol). Stir the mixture at room temperature overnight. Follow the reaction by TLC (hexane/EtOAc 9:1). Remove the solvent under vacuum. Dissolve the residue in EtOAc and wash with water. Dry the organic layer and concentrate. Preparation 17 is used without further purification.

PREPARATION 18



10 Add 4-(trifluoromethyl)benzonitrile (8.2 g, 48.08 mmol) and potassium *tert*-butoxide (1.62 g, 14.42 mmol) to a solution of preparation 17 (24.04 mmol) in EtOH (50 mL) and stir the mixture at reflux for 48 hours. Follow the reaction by TLC
15 (Hexane/EtOAc 4:1). Quench the crude with water and remove the MeOH in vacuo and extract the aqueous layer with EtOAc. Separate the organic layer, dry with MgSO₄, and concentrate in vacuum. Purify the crude by flash chromatography (Hexane/EtOAc 4:1 and 2:1) to obtain 2.5 g (22% yield) of preparation 18.

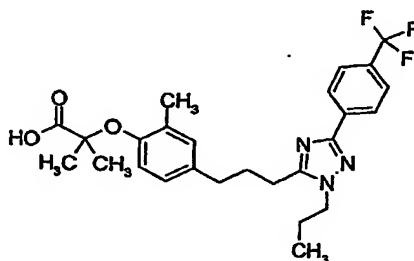
PREPARATION 19



20

Add powdered KOH (0.065 g, 1.16 mmol), PrI (0.10 mL, 1.04 mmol) and Bu₄NBr (0.033 g, 0.10 mmol) to a solution of preparation 18 (0.25 g, 0.52 mmol) in THF (5 mL) and stir the mixture at room temperature overnight. Follow the reaction by TLC (hexane/EtOAc 4:1). Quench the crude with water and add EtOAc. Extract the aqueous layer with EtOAc (2x). Separate the organic layer, dry with MgSO₄, and concentrate in vacuo. Purify the crude by flash chromatography (Hexane/EtOAc 9:1) to obtain 0.13 g (48% yield) of preparation 19.

EXAMPLE 54



10

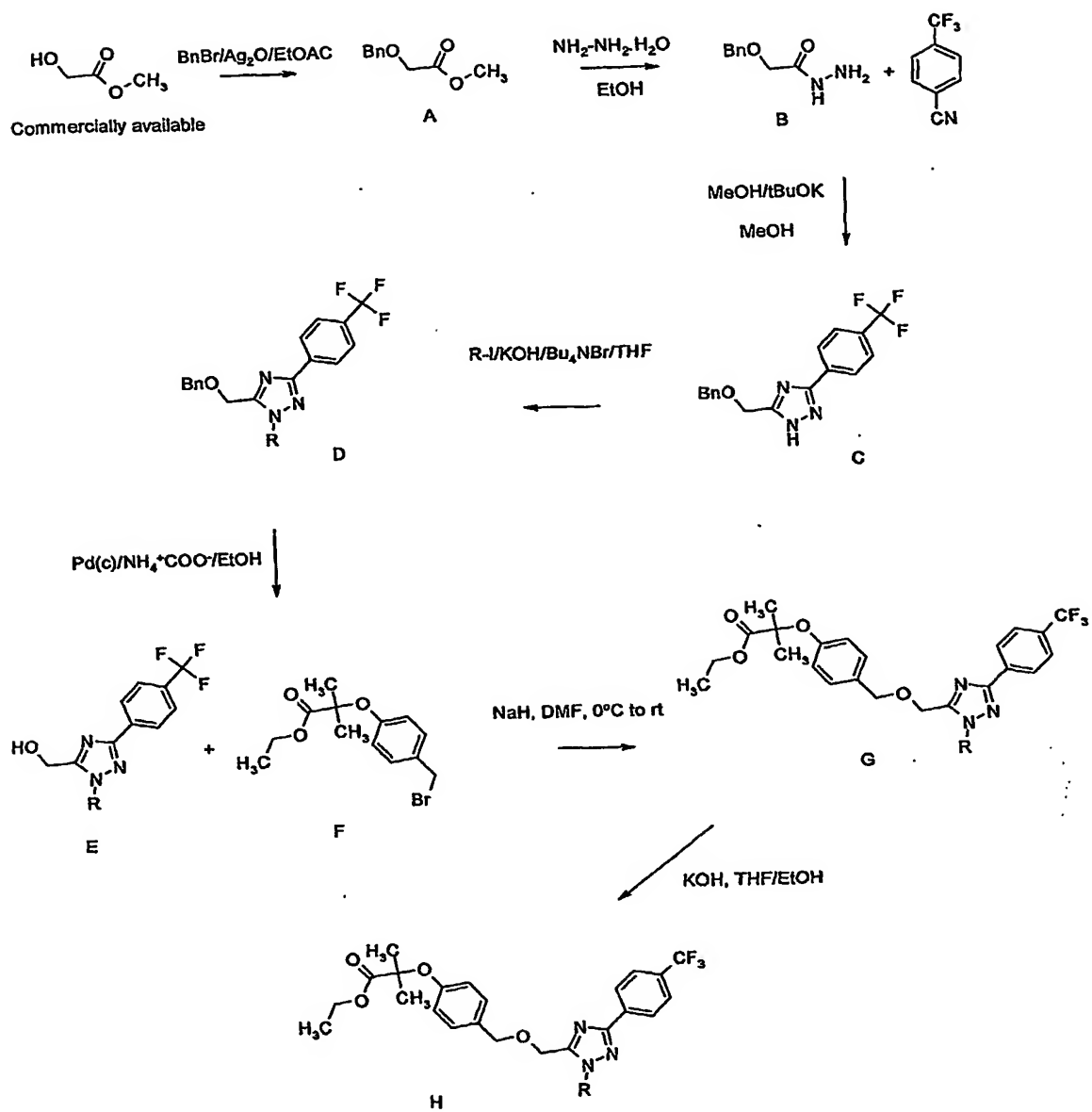
Add TFA (excess) to a solution of preparation 19 (0.09 g, 0.17 mmol) in CH₂Cl₂ (5 ml) and stir the mixture at room temperature overnight. Follow the reaction by TLC (Hexane/EtOAc 1:1). Remove the solvent and residual TFA in vacuum. Dissolve the residue in DCM and wash with a saturated solution of NaHCO₃. Dry the organic layer with MgSO₄ and concentrate in vacuum. Obtain example 54 as a solid, 0.06 g (72% yield).

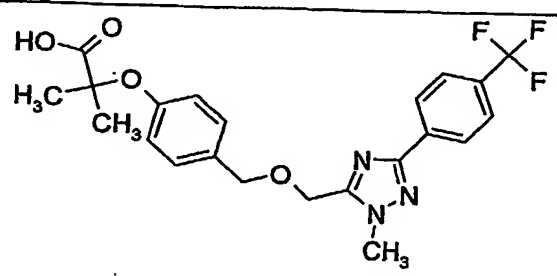
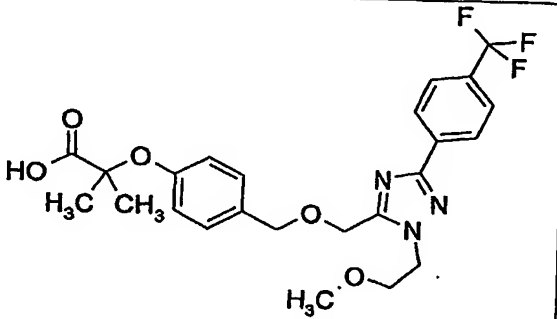
15

Example 53 is prepared by a similar procedure for the preparation of example 54.

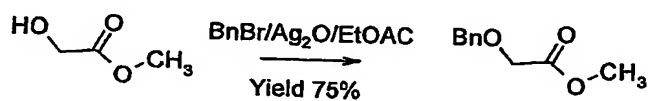
SCHEME 6

20



Example	Structure	LC/MS [M + 1]
55		450.1
56		494.2

GENERAL PROCEDURE FOR SCHEME 6



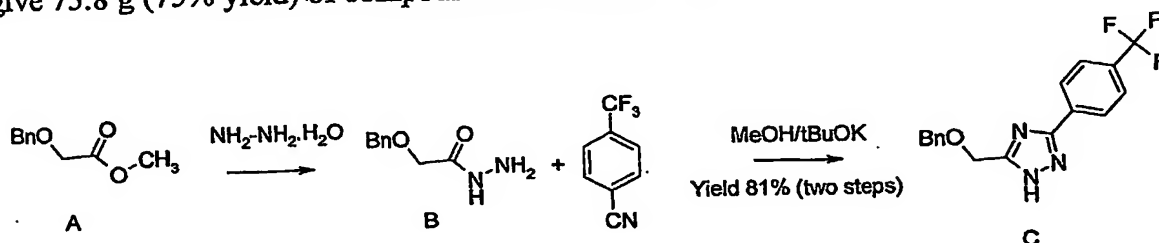
5

Commercially available

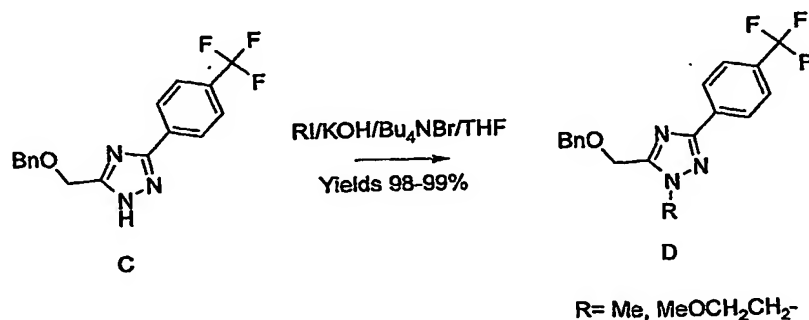
A

Add BnBr (72.7 mL, 0.61 mol, 1.1 eq) and Ag₂O (141.6 g, 0.61 mol, 1.1 eq) to a solution of methyl glycolate (50 g, 0.56 mol) in EtOAc (300 mL) and stir the mixture to reflux overnight. Follow the reaction by TLC (Hexane /EtOAc 1:1). Filter the reaction
 10 through celite and remove the solvent under vacuum. Pass adsorb the oil onto flash silica

and place on top of a pad of flash silica (500g) and elute with 20% ethyl acetate/hexane to give 75.8 g (75% yield) of compound A of scheme 6 as a colorless oil.



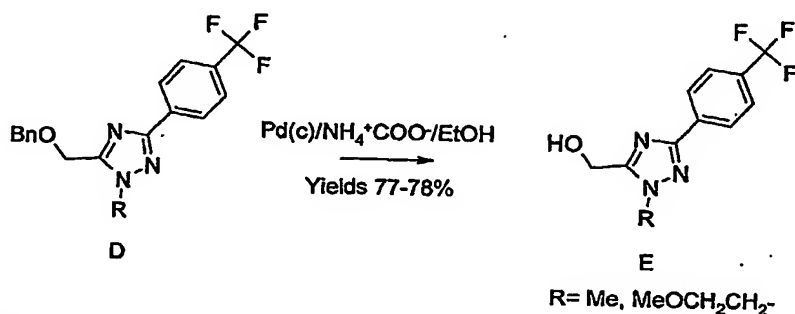
- 5 Dissolve the benzyl derivate compound of formula A of scheme 6 (1.0 mmol) in EtOH (0.8 M) and then add hydrazine monohydrate (3.0 mmol). Stir the mixture at room temperature overnight. Follow the reaction by TLC (hexane/EtOAc 4:1). Remove the solvent under vacuum. Dissolve the residue in EtOAc and wash with water. Dry the organic layer and concentrate and use the crude without further purification. Add 4-(trifluoromethyl)benzonitrile (2.0 mol) and potassium *tert*-butoxide (0.6 mmol) to a solution of acylhydrazine compound of formula B of scheme 6 (1.0 mmol) in MeOH (2.4 M) and stir the mixture at reflux for 24 hours. Follow the reaction by TLC (Hexane/EtOAc 4:1). Quench the crude with water, remove the MeOH in vacuum, and extract the aqueous layer with EtOAc. Separate the organic layer, dry with MgSO_4 , and concentrate in vacuum. Purify the crude by Biotage (Hexane/EtOAc 4:1) and obtain the compound C of scheme 6.



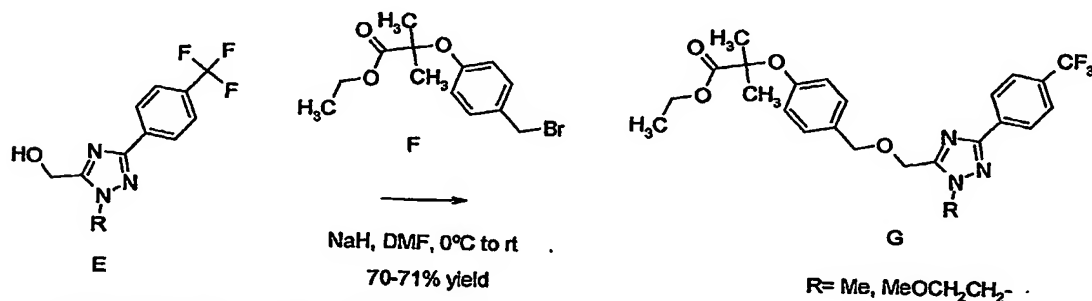
R = Me or $\text{MeOCH}_2\text{CH}_2$ -

- 20 **Triazole alkylation:** Add powdered KOH (2.2 mmol), R-I (Br) (2.0 mmol) and Bu_4NBr (0.2 mmol) to a solution of the corresponding triazole compound (C) of scheme 6 (1.0 mmol) in THF (5 mL/mmol) and stir the mixture at room temperature overnight. Follow the reaction by TLC (Hexane/EtOAc 4:1). Quench the crude with water and add

EtOAc. Extract the aqueous layer with EtOAc (2x). Separate the organic layer, dry with MgSO_4 , and concentrate in vacuum. Purify the crude by Biotage (Hexane/EtOAc 4:1) to obtain compound of formula D of scheme 6.

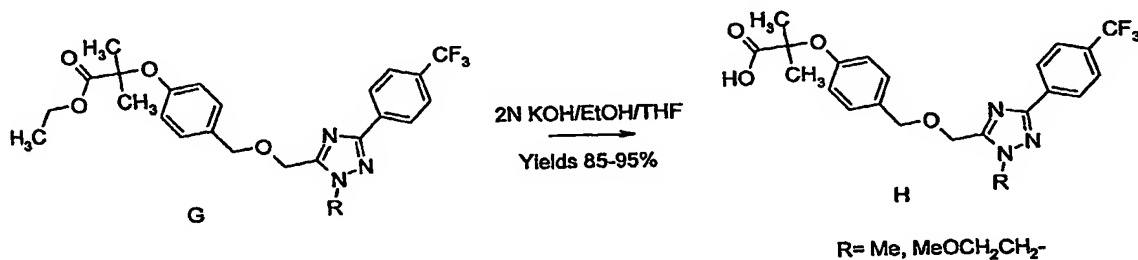


- 5 Add Pd (C) (10-20% in weight) and $\text{NH}_4^+\text{COO}^-$ (10-20 mmol) to a solution of triazole compound of formula D of scheme 6 (1.0 mmol) in EtOH (5 mL/mmol) and stir the mixture at 80°C overnight. Follow the reaction by TLC. Filter the reaction through celite and remove the solvent under vacuum. Purify the crude by Biotage
- 10 (Hexane/EtOAc 1:1) to obtain compound of formula E of scheme 6.



- 15 Add NaH (2.1 mmol, 60%) to a solution of triazole derivate compound of formula E of scheme 6 (1.0 mmol) in anhydrous DMF (10 mL) at 0°C , stir the mixture at room temperature for 15 minutes, cool to 0°C , and add the benzyl bromide (compound F of scheme 6) (1.5 mmol) in anhydrous DMF (5 mL). Stir the reaction at room temperature for 30 min, add MeOH, and then add water. Remove the MeOH in vacuum and extract

the aqueous layer with EtOAc. Wash the organic layer with water and brine, dry over MgSO_4 , filter, and concentrate under reduced pressure. Purify the crude by Biotage (Hexane/EtOAc 4:1) to obtain compound of formula G of scheme 6 as white solids.

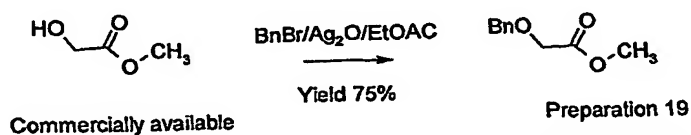


- 5 Add 2N KOH solution (10 mmol) to a solution of triazole derivate compound of formula G of scheme 6 (1.0 mmol) in EtOH/THF mixture (1:1) (10 mL/mmol) and stir the mixture at room temperature overnight. Follow the reaction by TLC. Remove the solvent under vacuum and then, add water and EtOAc. Add 1N HCl solution until pH 5-7.
- 10 7. Extract the mixture and wash the organic layer with water, separate, dry with MgSO_4 , and concentrate in vacuum. Obtain the products of compound of formula H of scheme 6 as white solids.

SYNTHESIS OF EXAMPLE 55

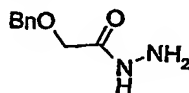
15

PREPARATION 19



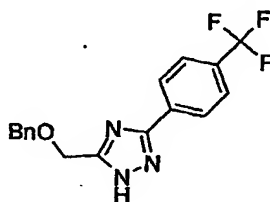
- 20 Add BnBr (72.7 mL, 0.61 mol, 1.1 eq) and Ag_2O (141.6 g, 0.61 mol, 1.1 eq) to a solution of methyl glycolate (50 g, 0.56 mol) in EtOAc (300 mL) and stir the mixture to reflux overnight. Follow the reaction by TLC (Hexane /EtOAc 1:1). Filter the reaction through celite and remove the solvent under vacuum. The oil is passed adsorbed onto flash silica. Place on top of a pad of flash silica (500g) and elute with 20% ethyl acetate/hexane to give 75.8 g (75% yield) of preparation 19 as a colorless oil.

PREPARATION 20



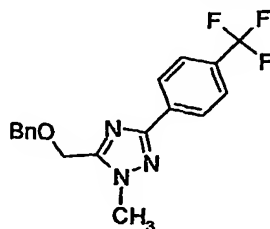
Dissolve preparation 19 (7.5 g, 41.6 mmol) in EtOH (100 mL). Then, add hydrazine monohydrate (6.05 mL, 124.9 mmol) and stir the mixture at room temperature overnight. Follow the reaction by TLC (hexane/EtOAc 4:1). Remove the solvent under vacuum. Dissolve the residue in EtOAc and wash with water. Dry the organic layer and concentrate. Use preparation 20 without further purification.

PREPARATION 21



Add 4-(trifluoromethyl)benzonitrile (14.2 g, 83.2 mmol) and potassium *tert*-butoxide (2.8 g, 25 mmol) to a solution of preparation 20 in MeOH (100 mL) and stir the mixture at reflux for 24 hours. Follow the reaction by TLC (Hexane/EtOAc 4:1). Quench the crude with water, remove the MeOH in vacuum and extract the aqueous layer with EtOAc. Separate the organic layer, dry with MgSO₄, and concentrate in vacuum. Purify the crude by flash chromatography (Hexane/EtOAc 4:1) to obtain 11.2 g (81% yield) of preparation 21 as a white solid.

PREPARATION 22

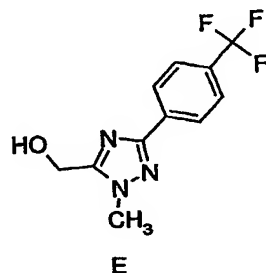


Add powdered KOH (0.27 g, 4.8 mmol), MeI (0.28 mL, 4.5 mmol) and Bu₄NBr (0.09 g, 0.3 mmol) to a solution of preparation 21 (1.0 g, 3.0 mmol) in THF (15 mL) and stir the mixture at room temperature overnight. Follow the reaction by TLC

(Hexane/EtOAc 4:1). Quench the crude with water and add EtOAc. Extract the aqueous layer with EtOAc (2x). Separate the organic layer, dry with MgSO_4 , and concentrate in vacuum. Purify the crude by Biotage (Hexane/EtOAc 4:1) to obtain preparation 22 (1.04 g).

5

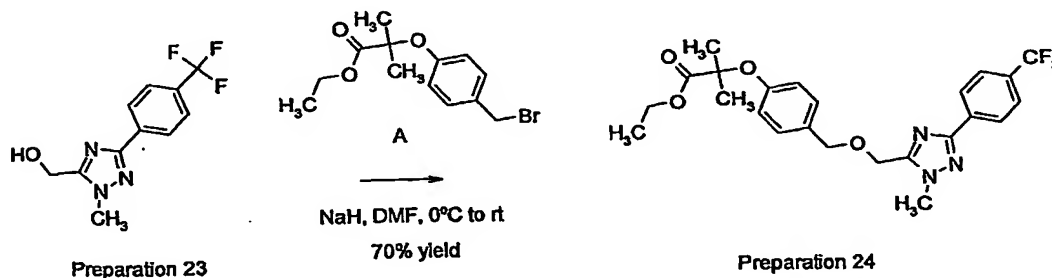
PREPARATION 23



Add Pd (C) (10-20% in weight) and $\text{NH}_4^+\text{COO}^-$ (1.89 g, 30 mmol) to a solution of preparation 22 (1.04 g, 3.0 mmol) in EtOH (15 mL) and stir the mixture at 80°C overnight. Follow the reaction by TLC. Filter the reaction through celite and remove the solvent under vacuum. Purify the crude by Biotage (Hexane/EtOAc 1:1) to obtain preparation 23 (0.59 g, 76% yield).

10

PREPARATION 24



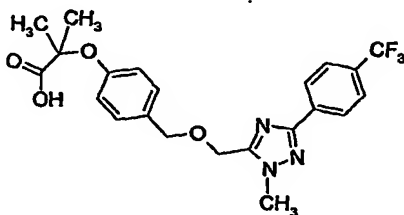
15

Add NaH (0.091 g, 2.29 mmol, 60%) to a solution of preparation 23 (0.28 g, 1.09 mmol) in anhydrous DMF (10 mL) at 0°C and stir the mixture at room temperature for 15 minutes. Cool again at 0°C and add the benzyl bromide compound A (0.68 g, 1.63 mmol) in anhydrous DMF (5 mL) and stir the reaction at room temperature for 30 min. Add MeOH and then add water. Remove the MeOH in vacuum and extract the aqueous layer with EtOAc. Wash the organic layer with water and brine, dry over MgSO_4 , filter and

20

concentrate under reduced pressure. Purify the crude by Biotage (Hexane/EtOAc 4:1) to obtain preparation 24 as white solids (0.39 g, 70% yield).

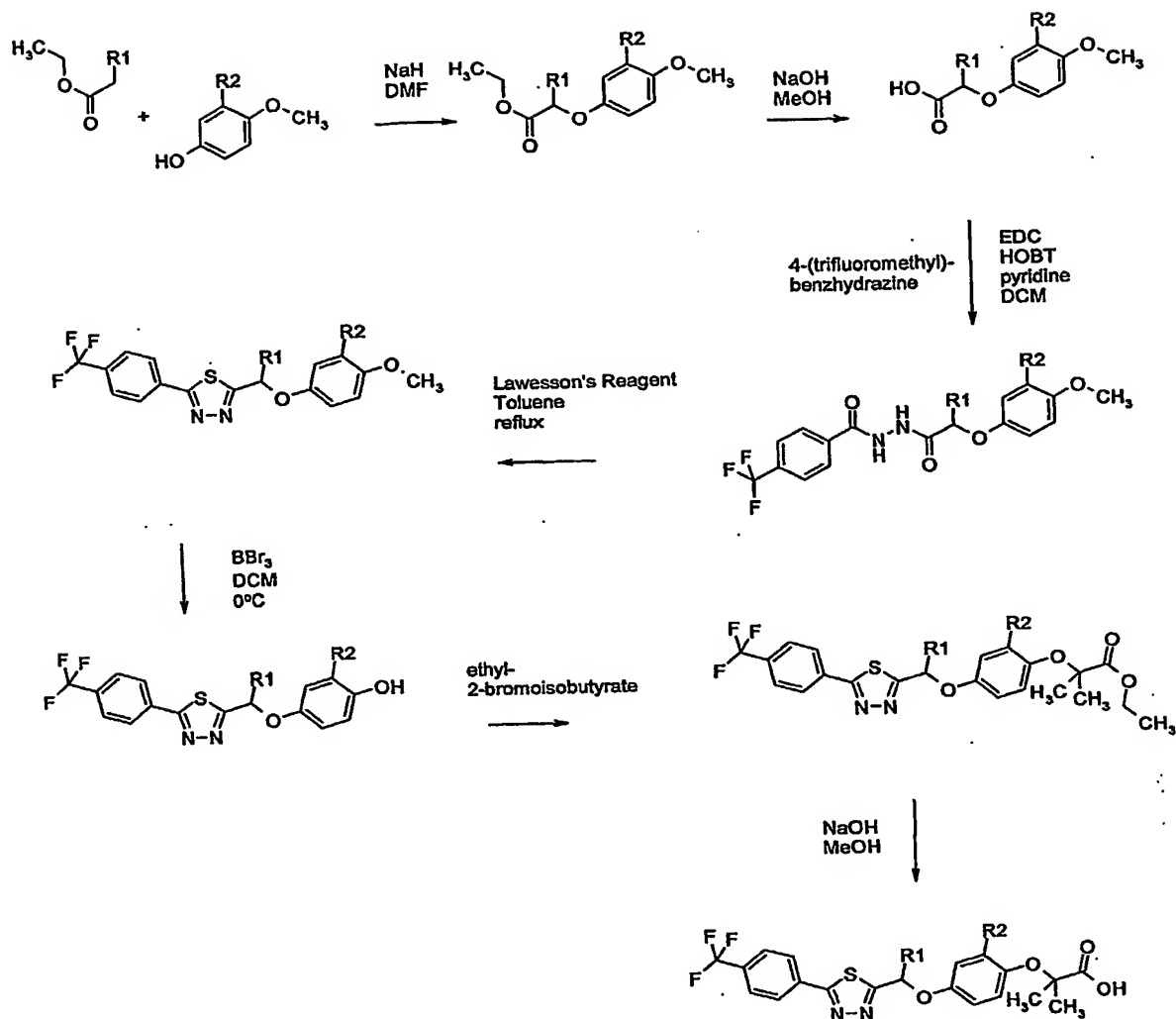
EXAMPLE 55



5 Add 2N KOH solution (1.05 mL, 2.1 mmol) to a solution of preparation 24 (0.1 g, 0.21 mmol) in EtOH/THF mixture (1:1) (2 mL) and stir the mixture at room temperature overnight. Follow the reaction by TLC. Remove the solvent under vacuum and then, add water and EtOAc. Add 1N HCl until pH 5-7. Extract the mixture and wash the organic
10 layer with water, separate, dry with MgSO₄, and concentrate in vacuum. Example 55 is obtained as white solids (65 mg, 69% yield).

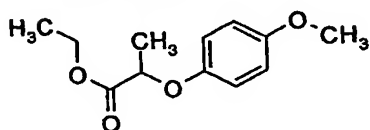
Example 56 is prepared by a similar procedure for the preparation of example 55.

SCHEME 7



5

PREPARATION 25



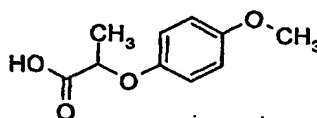
Slurry sodium hydride (369mg, 9.2mmol) in DMF (25ml) at 0°C , and then add 4-methoxyphenol (1.15g, 9.2mmol) in one portion. After stirring for 30 min., add ethyl 2-bromopropionate (1.391g, 7.7mmol) in one portion and allow the reaction to warm to

10

room temperature overnight. Quench the reaction with 1N HCl and extract with ethyl acetate. Combine the organic layers, dry over MgSO₄, and evaporate. Purify the residue via silica gel chromatography (30% ethyl acetate in hexanes) to give the 983.1mg of preparation 25 as a thick, clear oil (57.2%). MS = 225 (M+H⁺); 242 (M+NH₄⁺).

5

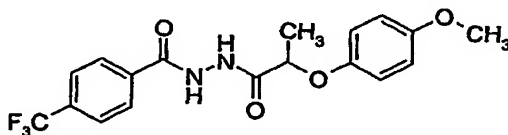
PREPARATION 26



Dissolve preparation 26 (983mg, 4.4mmol) in methanol (10ml) and add to this 1N NaOH (10ml). Stir at room temperature for 12 hrs. Then, evaporate the solvent, dissolve the residue in 1N HCl (20 ml), and extract with ethyl acetate. Combine the organics, dry over MgSO₄, and evaporate. Use this crude product (767.5mg, 89%) without further purification. MS = 195 (M-H⁻); 214 (M+NH₄⁺).

10

PREPARATION 27

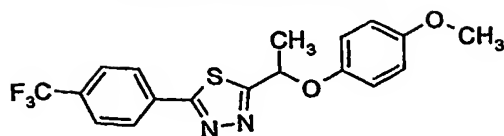


15

Dissolve preparation 26 (100mg, 0.5mmol) in dichloromethane (10ml) and add EDC (117mg, 0.6mmol) followed by HOBT (83mg, 0.6mmol) and stir for for 5 min. Then, add 4-(trifluoromethyl)benzhydrazine (104mg, 0.5mmol) in one portion followed by pyridine (0.124ml, 1.5mmol) and stir at room temperature overnight. After this time, wash the reaction with saturated sodium bicarbonate solution and 1N HCl. Dry the organics over MgSO₄ and evaporate. Purify the residue via silica gel chromatography (50% ethyl acetate in hexanes) to give the 127.8mg of preparation 27 as white solid (65.6%). MS = 383 (M+H⁺); 381 (M-H⁻).

20

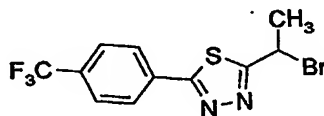
PREPARATION 28



Dissolve the preparation 27 (127mg, 0.33mmol) in toluene (5ml). To this add Lawesson's reagent (134mg, 0.33mmol) and heat the reaction to reflux for 2 hrs.

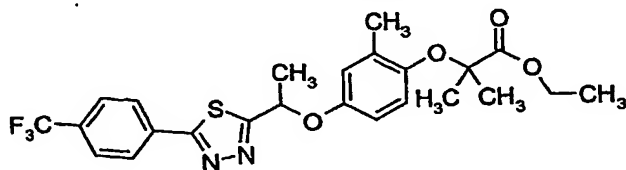
- 5 After this time, cool the reaction and dilute with 20ml of ethyl acetate. Wash with saturated bicarbonate solution and dry the organics over MgSO_4 and evaporate. Purify the residue via silica gel chromatography (15% ethyl acetate in hexanes) to give the 103.8mg of preparation 28 as a white solid (82.2%). MS = 381 ($\text{M}+\text{H}^+$).

PREPARATION 29



- 10 Dissolve preparation 28 (100mg, 0.26mmol) in dichloromethane (5ml). This is then cooled to 0°C and add boron tribromide (0.788ml, 0.79mmol). After 2 hrs, quench the reaction with saturated bicarb and extract with 20ml of ethyl acetate. The organics are dried over MgSO_4 and evaporated. This gave 87.2mg of preparation 29 as an off white solid (98.4%). MS = 337 & 338 ($\text{M}+\text{H}^+$).

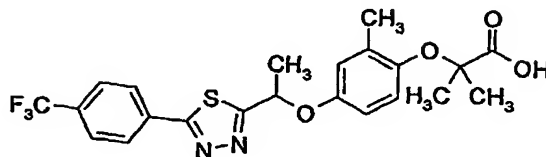
PREPARATION 30



- 20 Dissolve 2-(4-hydroxy-2-methyl-phenoxy)-2-methyl-propionic acid ethyl ester (73.6mg, 0.31mmol) in DMF. To this add sodium hydride (12.4mg, 0.31mmol) and stir at room temperature for 5 min. After this time preparation 29 (87mg, 0.26mmol) is added in one portion and the reaction continued for 2 hrs. Quench the reaction with saturated ammonium chloride and extract with ethyl acetate. Dry the organics over MgSO_4 and
- 25 evaporate. Purify the residue via silica gel chromatography (15% ethyl acetate in

hexanes) to give the 59.7mg of preparation 30 as a clear oil (46.8%). MS = 495 (M+H⁺).

EXAMPLE 57



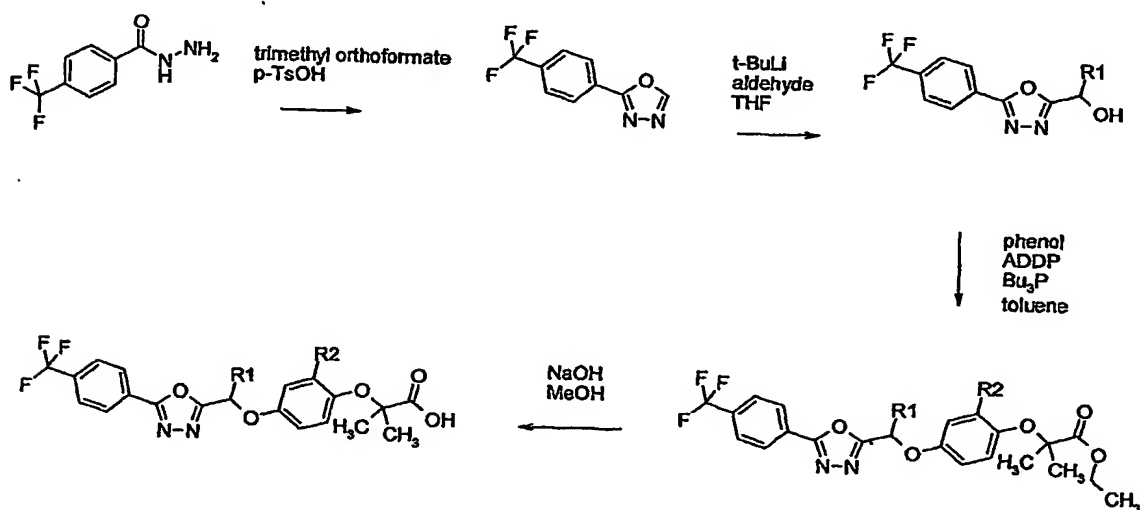
5

Dissolve preparation 30 (59mg, 0.12mmol) in methanol (2ml). To this, add 1N NaOH solution (2ml). After 12 hrs the reaction is brought to pH=6 with 1N HCl solution and extracted ethyl acetate. Dry the organics over MgSO₄ and evaporate. Purify the residue via silica gel chromatography (50% ethyl acetate in hexanes) then reverse phase HPLC (40-90% gradient @ 140 ml/min for 30 min on a 50 x 250mm, mm, C18 Symmetry column) to give the 7.1mg of example 57 as a white solid (12.7%). MS = 467 (M+H⁺).

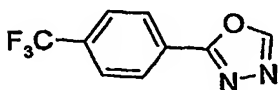
10

SCHEME 8

15

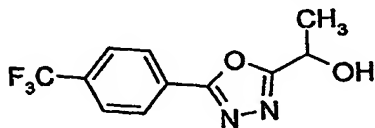


PREPARATION 31



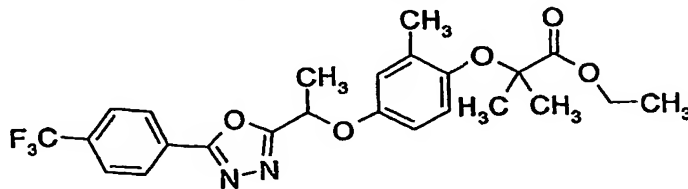
- Place 4-(Trifluoromethyl)benzhydrazone (5g, 24.5mmol) in a round bottom flasks equipped with a short path reflux condenser. Add to this was trimethyl orthoformate (4ml, 36.7mmol) followed by p-toluene sulfonic acid (46.6mmg, 0.24mmol). Heat to 100°C and distill off the methanol. After 2 hrs, no more methanol is collected the pressure of the system is lowered to 300 microns to remove the unused trimethyl orthoformate. Cool the residual solid and dissolve in ethyl acetate. Wash with saturated bicarbonate solution and combine the organics, dry over MgSO₄, and evaporate.
- 10 Use the crude product (5.2g, 99%) without further purification. MS = 215 (M+H⁺).

PREPARATION 32



- Dissolve preparation 31 (500mg, 2.3mmol) in THF and cool to -78°C. To this, add t-BuLi (1.5ml, 1.7M soln) and stir for 30 min. After this time, add acetaldehyde (0.157ml, 2.8mmol) and allow the reaction to slowly warm to room temperature over 6 hrs. After this time, quench the reaction with saturated ammonium chloride solution and then extract with ethyl acetate. Dry the combined organics over MgSO₄ and evaporate. Purify the residue via silica gel chromatography (20% ethyl acetate in hexanes) to give
- 20 24mg of preparation 32 as white solid (3.9%).

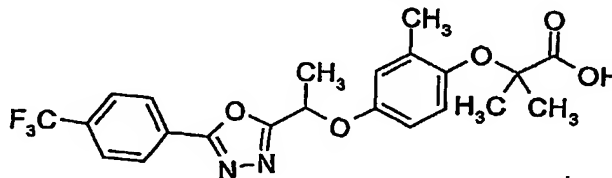
PREPARATION 33



- Dissolve preparation 32 (24mg, 0.09mmol) in toluene (2ml) and add 2-(4-hydroxy-2-methyl-phenoxy)-2-methyl-propionic acid ethyl ester (26.5mg, 0.11mmol).
- 25

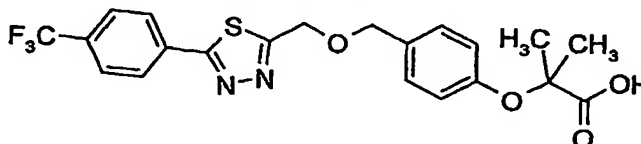
Bubble nitrogen into this mixture for 15min. After this time, add ADDP (35.1mg, 0.135mmol) followed by Bu_3P (0.034ml, 0.135mmol) and stir the reaction for 18hrs at room temperature. After this time, dilute the reaction in 20 ml of ethyl acetate and wash with brine. Dry the organics over MgSO_4 and evaporate. Purify the residue via silica gel chromatography (20% ethyl acetate in hexanes) to give 24.4mg of preparation 33 as a white solid (54.9%). $\text{MS} = 479 (\text{M}+\text{H}^+)$.

EXAMPLE 58



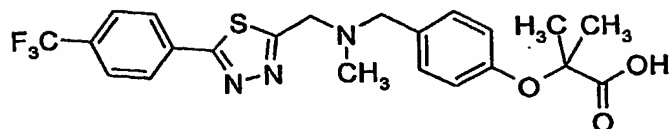
Dissolve the preparation 33 (59mg, 0.12mmol) in methanol (2ml). To this, add 1N NaOH solution (2ml). After 12 hrs the reaction is brought to pH=6 with 1N HCl solution and extracted ethyl acetate. Dry the organics over MgSO_4 and evaporate. Purify the residue via silica gel chromatography (50% ethyl acetate in hexanes) then reverse phase HPLC (40-90% gradient @ 140 ml/min for 30 min on a 50 x 250mm, mm, C18 Symmetry column) to give the 8.6mg of example 58 as a white solid (9.5%). $\text{MS} = 451 (\text{M}+\text{H}^+)$.

EXAMPLE 59



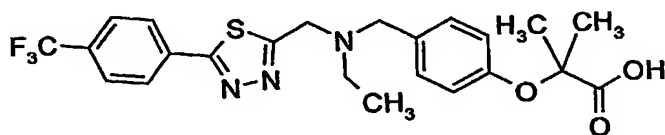
Example 59 can be made by one of ordinary skill in the art using the same procedure as example 57 using 2-(4-hydroxymethyl-phenoxy)-2-methyl-propionic acid ethyl ester (162mg, 0.67mmol) as the nucleophile and 2-bromomethyl-5-(4-trifluoromethyl-phenyl)-[1,3,4]thiadiazole (200mg, 0.62mmol) as the electrophile (as described in preparation 30) and then doing the saponification as described in example 57. After purification via silica gel chromatography (20% ethyl acetate in hexanes), 60.2mg (21.5%) of example 59 is obtained as a thick oil. $\text{MS} = 451 (\text{M}-\text{H})$.

EXAMPLE 60



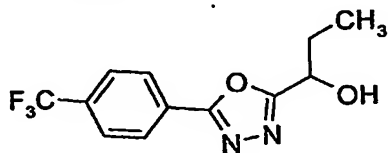
Example 60 can be made by one of ordinary skill in the art using the same
 5 procedure as example 57 using 2-Methyl-2-(4-methylaminomethyl-phenoxy)-propionic
 acid ethyl ester (171mg, 0.67mmol) as the nucleophile and 2-bromomethyl-5-(4-
 trifluoromethyl-phenyl)-[1,3,4]thiadiazole (200mg, 0.62mmol) as the electrophile (as
 described in preparation 30) and then doing the saponification as described in example
 57. After purification via silica gel chromatography (10% methanol in dichloromethane),
 10 75.3mg (26.3%) of example 60 is obtained as a thick oil. MS = 464 (M-H).

EXAMPLE 61



Example 61 can be made by one of ordinary skill in the art using the same
 15 procedure as example 57 using 2-(4-Ethylaminomethyl-phenoxy)-2-methyl-propionic
 acid ethyl ester (180.6mg, 0.67mmol) as the nucleophile and 2-bromomethyl-5-(4-
 trifluoromethyl-phenyl)-[1,3,4]thiadiazole (200mg, 0.62mmol) as the electrophile (as
 described in preparation 30) and then doing the saponification as described in example
 57. After purification via silica gel chromatography (10% methanol in dichloromethane),
 20 24.3mg (8.3%) of example 61 is obtained as a thick oil. MS = 478 (M-H).

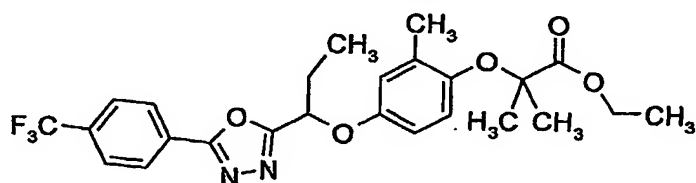
PREPARATION 34



Dissolve preparation 31 (500mg, 2.3mmol) in THF and cool to -78°C. To this,
 25 add t-BuLi (1.5ml, 1.7M soln) and stir for 30 min. After this time, add propionaldehyde

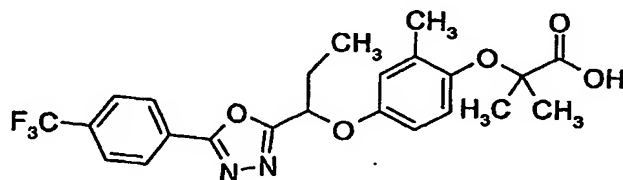
(0.202ml, 2.8mmol) and allow the reaction to slowly warm to room temperature over 6 hrs. After this time, quench the reaction with saturated ammonium chloride solution and then extract with ethyl acetate. Dry the combined organics over MgSO₄ and evaporate. Purify the residue via silica gel chromatography (20% ethyl acetate in hexanes) to give
5 99.8mg of preparation 34 as white solid (15.7%).

PREPARATION 35



Dissolve preparation 34 (99mg, 0.36mmol) in toluene (5ml) and add 2-(4-
10 hydroxy-2-methyl-phenoxy)-2-methyl-propionic acid ethyl ester (105mg, 0.43mmol).
Bubble nitrogen into this mixture for 15min. After this time, add ADDP (139mg,
0.54mmol) followed by Bu₃P (111.5mg, 0.54mmol) and stir the reaction for 18hrs at
room temperature. After this time, dilute the reaction in 20 ml of ethyl acetate and wash
with brine. Dry the organics over MgSO₄ and evaporate. Purify the residue via silica gel
15 chromatography (20% ethyl acetate in hexanes) to give 63.0mg of preparation 35 as a
white solid (34.8%). MS = 493 (M+H⁺).

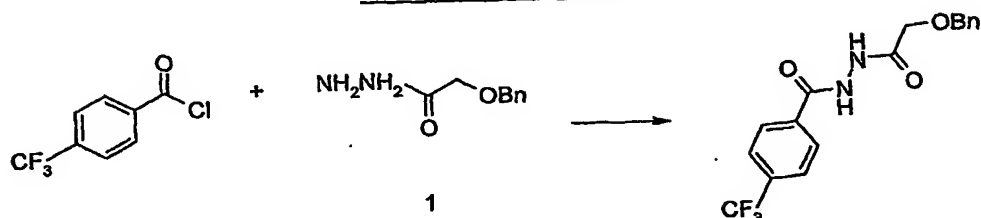
EXAMPLE 62



20 Dissolve the preparation 35 (63mg, 0.13mmol) in methanol (2ml). To this is then
added 1N NaOH solution (2ml). After 12 hrs the reaction is brought to pH=6 with 1N
HCl solution and extracted ethyl acetate. The organics are dried over MgSO₄ and
evaporated. Purify the residue via silica gel chromatography (50% ethyl acetate in
hexanes) then reverse phase HPLC (40-90% gradient @ 140 ml/min for 30 min on a 50 x

250mm, mm, C18 Symmetry column) to give the 9.7mg of example 62 as a white solid (16.3%). MS = 465 (M+H⁺).

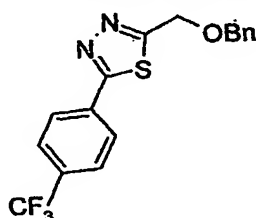
PREPARATION 36



5 Add p-trifluoromethyl benzoyl chloride (11.3 mL, 76 mmol) to a 0°C solution of the acyl hydrazine (compound 1 above) (13.7 g, 76 mmol) in CH₂Cl₂ (200 mL) and pyridine (20 mL) over 15 min and stir the reaction for 30 min. Then, pour into 5N HCl (200 mL). Extract the solution with Et₂O (250 mL) and EtOAc (250 mL). Wash the
10 combined organic extracts with H₂O (200 mL) followed by brine (200 mL), dry over Na₂SO₄, filter, and concentrate. Titrate the crude semisolid with 10% Et₂O /hexanes, precipitating out the desired Preparation 36 (23.4 g, 88%) as a white solid. ¹H NMR (CDCl₃) δ 10.64 (s, 1 H), 10.07 (s, 1 H), 8.09 (m, 2 H), 7.93 (m, 2 H), 7.40 (m, 5 H), 4.64 (s, 2 H), 4.11 (s, 2 H).

15

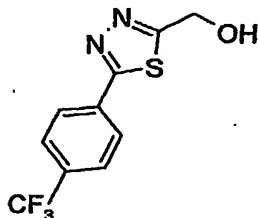
PREPARATION 37



Heat a solution of Preparation 36 (12.0 g, 34.1 mmol) and Lawesson's reagent (16.5 g, 40.9 mmol) in toluene (200 mL) to reflux for 4 hr, then cool to room temperature
20 and pour into H₂O (400 mL). Extract the mixture with Et₂O (200 mL) and EtOAc (400 mL). Wash the combined organic extracts with brine (250 mL), dry over Na₂SO₄, filter, and concentrate. Purification of the crude product by MPLC (0% to 10% to 15% to 20% EtOAc/hexanes gradient) affords Preparation 37 (11.2 g, 93%) as a clear oil. ¹H NMR

(CDCl₃) δ 8.10 (d, J = 8.4 Hz, 2 H), 7.75 (d, J = 8.4 Hz, 2 H), 7.37 (m, 5 H), 4.99 (s, 2 H), 4.70 (s, 2 H).

PREPARATION 38

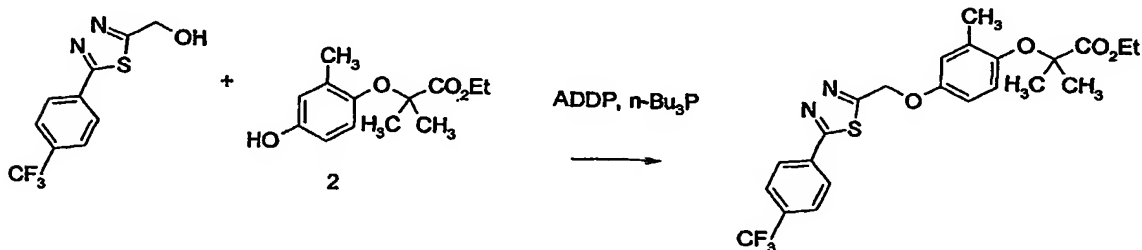


5

Add a solution of BBr₃ (42 mL, 1 M in CH₂Cl₂, 42 mmol) over 15 min. to a 0°C solution of Preparation 37 (9.8 g, 27.9 mmol) in CH₂Cl₂ (120 mL). After an additional 15 min at 0°C, pour the contents into ½ satd. NaHCO₃ (500 mL). Extract the mixture with Et₂O (250 mL) and EtOAc (300 mL). Wash the combined organic extracts with brine (250 mL), dry over Na₂SO₄, filter, and concentrate to afford a white solid. Titrate the crude product with 10% Et₂O/hexanes, precipitating out the desired Preparation 38 (7.0 g, >95%) as a white solid. ¹H NMR (CDCl₃) δ 8.09 (d, J = 8.4 Hz, 2 H), 7.60 (d, J = 8.4 Hz, 2 H), 5.16 (s, 2 H), 2.40-2.60 (br s, 1 H).

15

PREPARATION 39

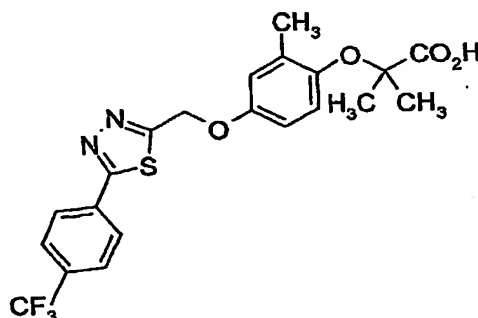


Bubble nitrogen gas through a solution of Preparation 38 (0.125 g, 0.48 mmol) and phenol 2 (0.119 g, 0.50 mmol) in toluene (5 mL) for 10 min. Cool the solution to 0°C and add tri-n-butyl phosphine (0.180 mL, 0.72 mmol) followed by (1,1'-azodicarbonyl-dipiperidine (ADDP) (0.182 g, 0.72 mmol). After 5 min, allow the reaction to warm to room temperature and stir for 16 hours. Then, pour the reaction mixture into ½ satd. NaHCO₃ (25 mL). Extract the mixture with Et₂O (25 mL) and EtOAc (25 mL). Wash the combined organic extracts with brine (25 mL), dry over

20

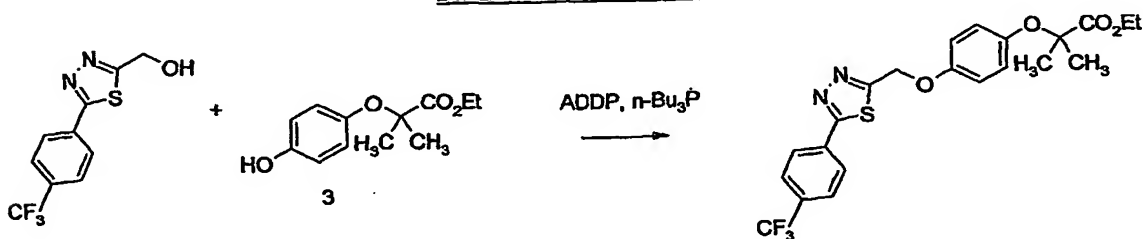
Na₂SO₄, filter, and concentrate. Purification of the crude product by MPLC (0% to 5% to 8% to 12% EtOAc/hexanes) affords preparation 39 (0.138 g, x%) as a white foam. ¹H NMR (CDCl₃) δ 8.11 (d, J = 8.4 Hz, 2 H), 7.77 (d, J = 8.4 Hz, 1 H), 6.72 (s, 1 H), 6.65 (m, 1 H), 6.56 (d, J = 3.2 Hz, 1 H), 5.48 (s, 2 H), 4.27 (q, J = 7.2 Hz, 2 H), 2.19 (s, 3 H), 1.55 (s, 6 H), 1.32 (t, J = 7.2 Hz, 3 H).

EXAMPLE 63



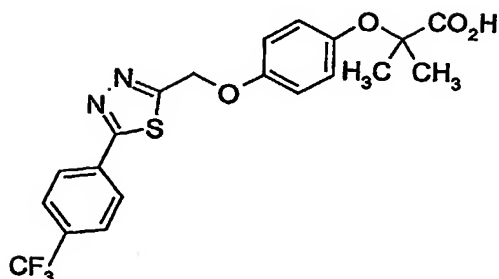
Heat a solution of Preparation 39 (0.138 g, 0.29 mmol) in EtOH (5 mL) and 2 N NaOH (1 mL) to 40°C for 1 h. Pour the mixture into 1 N HCl (20 mL) and extract with Et₂O (20 mL) and EtOAc (2 x 20 mL). Wash the combined organic extracts with brine (25 mL), dry over Na₂SO₄, filter, and concentrate. Purification of the crude product by column chromatography (35% EtOAc/2% HOAc in hexanes) affords example 59 (0.102 g, 77%) as a white solid. LRMS 453.1 (M⁺ + H).

PREPARATION 40



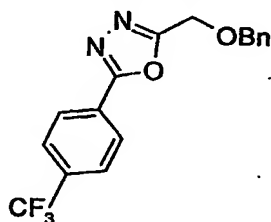
The reaction is run according to preparation 39. The reaction of Preparation 38 (0.125 g, 0.48 mmol) and phenol 3 (above) (0.112 g, 0.50 mmol) affords Preparation 40 (0.124 g, 55%) as a white foam. ¹H NMR (CDCl₃) δ 8.08 (d, J = 8.2 Hz, 2 H), 7.74 (d, J = 8.2 Hz, 2 H), 6.89 (m, 2 H), 6.75 (m, 2 H), 5.47 (s, 2 H), 4.23 (q, J = 7.2 Hz, 2 H), 1.52 (s, 6 H), 1.27 (t, J = 7.2 Hz, 3 H).

EXAMPLE 64



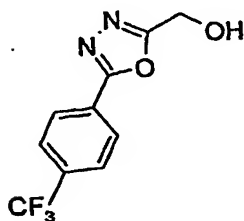
The reaction is run according to that for example 63. Hydrolysis of preparation 40 (0.124 g, 0.27 mmol) affords example 60 (0.082 g, 69%) as a white foam. LRMS 439.1 (M⁺ + H).

PREPARATION 41



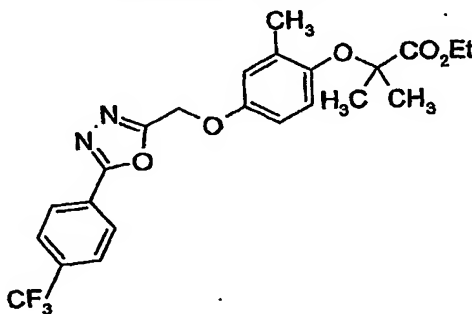
Bubble HCl (g) through a 0°C solution of p-trifluoromethylbenzonitrile (5.50 g, 32.1 mmol) in EtOH (9.4 mL, 161 mmol) and toluene (50 mL) for 30 min. Remove the cooling bath and maintain the solution at room temperature for 16 h. Concentration of the mixture affords the intermediate imidate salt, which is added to o-xylenes (165 mL). Add the acyl hydrazine 1 (procedure for preparation 36) (5.78 g, 32.1 mmol) as a solution in o-xylenes (10 mL). Add Et₃N (4.47 mL, 32.1 mmol) dropwise over 30 min, stir the solution for 2 hours, heat to reflux for 2.5 hours, cool to room temperature and maintain for 16 hours. Pour the solution into ½ satd. NaHCO₃ (250 mL) and extract with EtOAc (2 x 200 mL). Wash the combined organic extracts with brine (250 mL), dry over Na₂SO₄, filter, and concentrate. Purification of the crude product by column chromatography (0% to 15% to 20% to 25% to 35% EtOAc/hexanes) affords preparation 41 (0.53 g, 5%) as a white solid. ¹H NMR (CDCl₃) δ 7.79 (d, J = 8.0 Hz, 2 H), 7.72 (d, J = 8.0 Hz, 2 H), 7.30-7.40 (m, 5 H), 4.83 (s, 2 H), 4.70 (s, 2 H).

PREPARATION 42



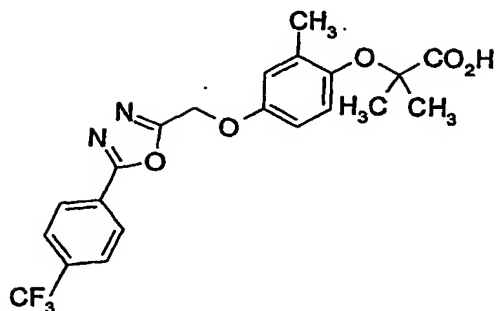
Expose a 40°C solution of Preparation 41 (0.53 g, 1.59 mmol) and 10% Pd-C (0.10 g) in MeOH (30 mL) and THF (10 mL) to 40 psi H₂ (g) for 24 h. Flushing of the mixture with N₂ (g) followed by filtration through celite provides a clear solution, which is concentrated to afford preparation 42 (0.24 g, 62%) as a white solid. ¹H NMR (CDCl₃) δ 8.18 (d, J = 8.0 Hz, 2 H), 7.70 (d, J = 8.0 Hz, 2 H), 5.00 (s, 2 H).

PREPARATION 43



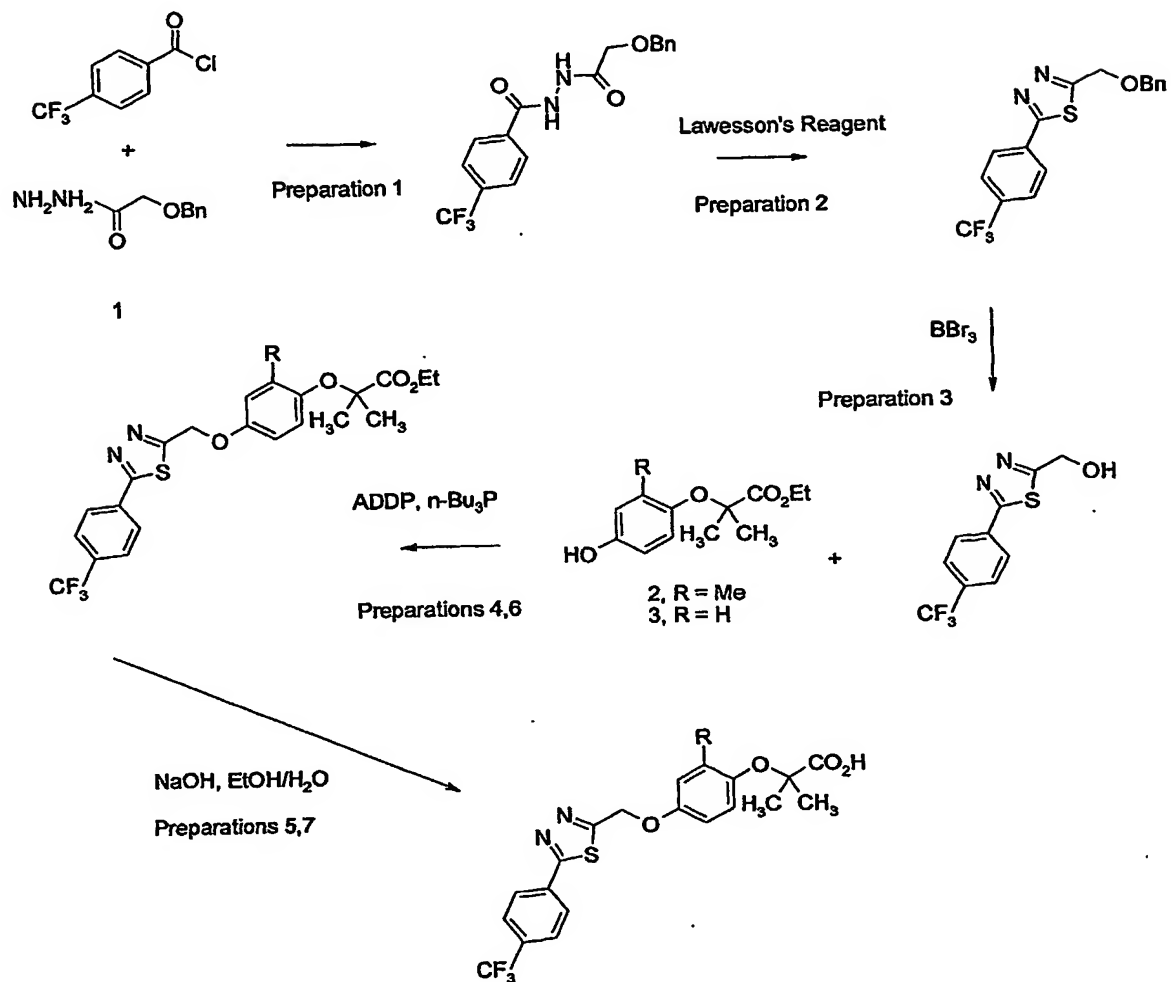
Preparation 43 is produced from preparation 42 (0.050 g, 0.20 mmol) and phenol 2 (0.051 g, 0.21 mmol) according to Preparation 39, affording preparation 43 (0.072 g, 76%) as a clear oil. ¹H NMR (CDCl₃) δ 8.20 (d, J = 8.4 Hz, 2 H), 7.78 (d, J = 8.4 Hz, 2 H), 6.85 (s, 1 H), 6.68 (m, 2 H), 5.27 (s, 2 H), 4.25 (q, J = 7.2 Hz, 2 H), 2.22 (s, 3 H), 1.54 (s, 6 H), 1.28 (t, J = 7.2 Hz, 3 H).

EXAMPLE 65

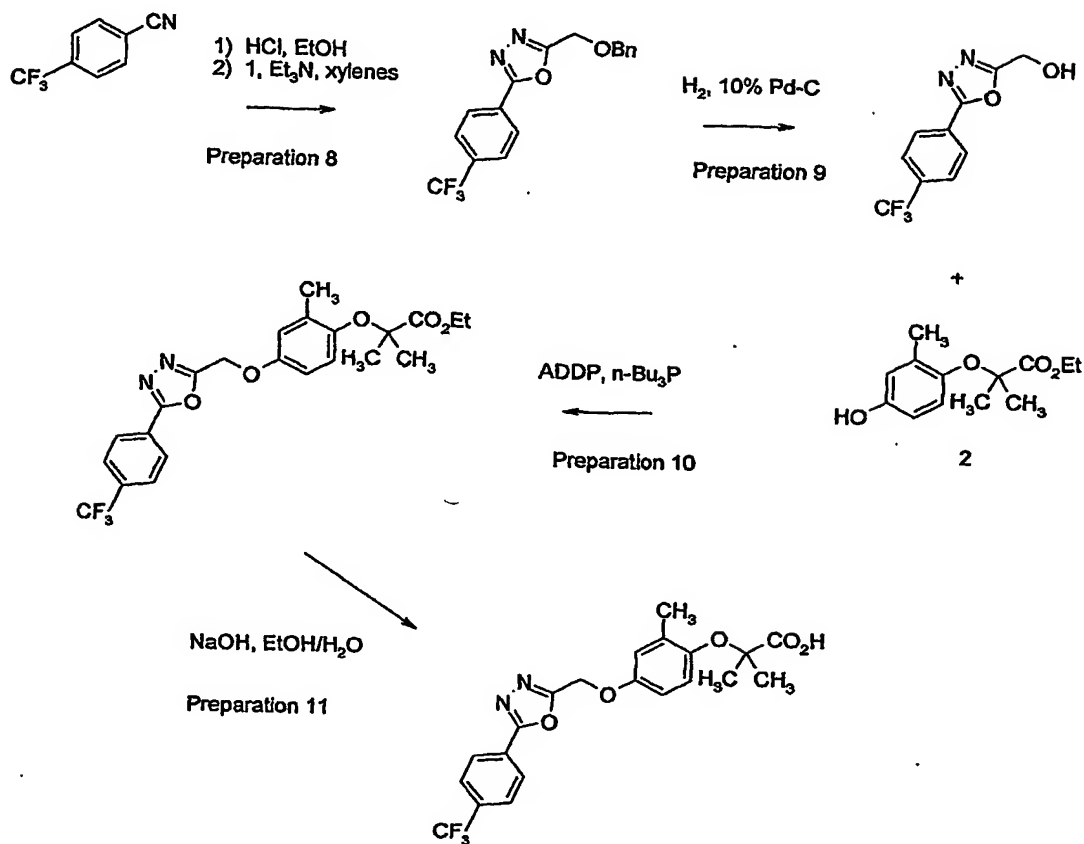


Example 65 is produced from preparation 43 according to the procedure for making example 63, affording example 65 (0.070 g, >95%) as a white solid. LRMS 455.1
5 (M+ + H).

SYNTHETIC SCHEME FOR THIADIAZOLES:

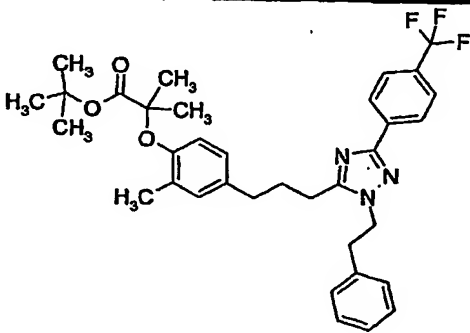
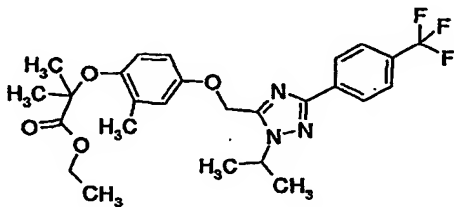
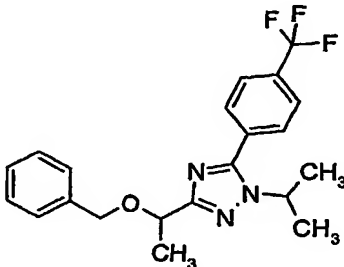


SYNTHETIC SCHEME FOR OXADIAZOLES:

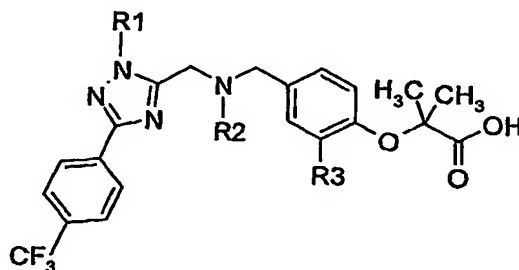


Compound	Structure	NMR Confirmation
Preparation 44		Proton, 2D-COSY, 2D-HSQC and 2D-HMBC at 500 MHz
Example 66		Proton, 2D-COSY, 2D-HSQC and 2D-HMBC at 500 MHz

Compound	Structure	NMR Confirmation
Preparation 45		Proton, 2D-COSY, 2D-HSQC and 2D-HMBC at 500 MHz
Example 67		Proton, 2D-COSY, 2D-HSQC and 2D-HMBC at 500 MHz
Preparation 46		Proton, 2D-COSY, 2D-HSQC and 2D-HMBC at 500 MHz
Preparation 47		Proton, 2D-COSY, 2D-HSQC and 2D-HMBC at 500 MHz
Preparation 48		Proton, 2D-COSY, 2D-HSQC and 2D-HMBC at 500 MHz
Preparation 49		Proton, 2D-COSY, 2D-HSQC and 2D-HMBC at 500 MHz

Compound	Structure	NMR Confirmation
Preparation 50		Proton and 1D-NOESY experiments at 500 MHz
Preparation 51		Proton, 2D-COSY, 2D-HSQC, 2D-HMBC and 1D-NOESY at 500 MHz
Preparation 51 Minor isomer was isolated		Proton and 1D-NOESY experiments at 500 MHz

EXAMPLE 67

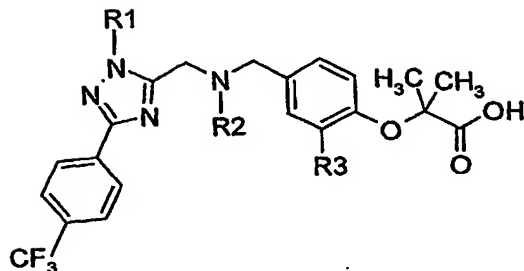


5 R3 = H, CH3

R2 = CH3, H

R1 = CH3, CH3CH2, CH(CH3)2

EXAMPLE 68



R₃ = CH₃

5 R₂ = CH₃, H

R₁ = CH₃, CH₃CH₂, CH(CH₃)₂

BIOLOGICAL ASSAYS

10 Binding and Cotransfection Studies

The in vitro potency of compounds in modulating PPAR α receptors are determined by the procedures detailed below. DNA-dependent binding (ABCD binding) is carried out using SPA technology with PPAR receptors. Tritium-labeled PPAR α agonists are used as radioligands for generating displacement curves and IC₅₀ values with
15 compounds of the invention. Cotransfection assays are carried out in CV-1 cells. The reporter plasmid contained an acylCoA oxidase (AOX) PPRE and TK promoter upstream of the luciferase reporter cDNA. Appropriate PPARs are constitutively expressed using plasmids containing the CMV promoter. For PPAR α , interference by endogenous PPAR γ in CV-1 cells is an issue. In order to eliminate such interference, a GAL4
20 chimeric system is used in which the DNA binding domain of the transfected PPAR is replaced by that of GAL4, and the GAL4 response element is utilized in place of the AOX PPRE. Cotransfection efficacy is determined relative to PPAR α agonist reference molecules. Efficacies are determined by computer fit to a concentration-response curve, or in some cases at a single high concentration of agonist (10 μ M).

25 These studies are carried out to evaluate the ability of compounds of the invention to bind to and/or activate various nuclear transcription factors, particularly huPPAR α ("hu" indicates "human"). These studies provide in vitro data concerning efficacy and

selectivity of compounds of the invention. Furthermore, binding and cotransfection data for compounds of the invention are compared with corresponding data for marketed compounds that act on huPPAR α .

5 The binding and cotransfection efficacy values for compounds of the invention which are especially useful for modulating a PPAR receptor, are ≤ 100 nM and $\geq 50\%$, respectively.

Evaluation of Triglyceride Reduction and HDL Cholesterol Elevation in HuapoAI Transgenic Mice

10 Compounds of the present invention are studied for effects upon HDL and triglyceride levels in human apoAI mice. For each compound tested, seven to eight week old male mice, transgenic for human apoAI (C57BL/6-tgn(apoal)¹rub, Jackson Laboratory, Bar Harbor, ME) are acclimated in individual cages for two weeks with standard chow diet (Purina 5001) and water provided ad libitum. After the acclimation,
15 mice and chow are weighed and assigned to test groups ($n = 5$) with randomization by body weight. Mice are dosed daily by oral gavage for 8 days using a 29 gauge, 1-1/2 inch curved feeding needle (Popper & Sons). The vehicle for the controls, test compounds and the positive control (fenofibrate 100mg/kg) is 1% carboxymethylcellulose (w/v) with 0.25% tween 80 (w/v). All mice are dosed daily between 6 and 8 a.m. with a dosing
20 volume of 0.2ml. Prior to termination, animals and diets are weighed and body weight change and food consumption are calculated. Three hours after last dose, mice are euthanized with CO₂ and blood is removed (0.5-1.0 ml) by cardiac puncture. After sacrifice, the liver, heart, and epididymal fat pad are excised and weighed. Blood is permitted to clot and serum is separated from the blood by centrifugation.
25 Cholesterol and triglycerides are measured colorimetrically using commercially prepared reagents (for example, as available from Sigma #339-1000 and Roche #450061 for triglycerides and cholesterol, respectively). The procedures are modified from published work (McGowan M. W. et al., Clin Chem 29:538-542,1983; Allain C. C. et al., Clin Chem 20:470-475,1974. Commercially available standards for triglycerides and
30 total cholesterol, respectively, commercial quality control plasma, and samples are measured in duplicate using 200 μ l of reagent. An additional aliquot of sample, added to

a well containing 200 µl water, provided a blank for each specimen. Plates are incubated at room temperature on a plate shaker and absorbance is read at 500 nm and 540 nm for total cholesterol and triglycerides, respectively. Values for the positive control are always within the expected range and the coefficient of variation for samples is below 10%. All
5 samples from an experiment are assayed at the same time to minimize inter-assay variability.

Serum lipoproteins are separated and cholesterol quantitated by fast protein liquid chromatography (FPLC) coupled to an in line detection system. Samples are applied to a Superose 6 HR size exclusion column (Amersham Pharmacia Biotech) and eluted with
10 phosphate buffered saline-EDTA at 0.5 ml/min. Cholesterol reagent (Roche Diagnostics Chol/HP 704036) at 0.16ml/min mixed with the column effluent through a T-connection and the mixture passed through a 15 m x 0.5 mm id knitted tubing reactor immersed in a 37 C water bath. The colored product produced in the presence of cholesterol is monitored in the flow stream at 505 nm and the analog voltage from the monitor is
15 converted to a digital signal for collection and analysis. The change in voltage corresponding to change in cholesterol concentration is plotted vs time and the area under the curve corresponding to the elution of very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL) is calculated using Perkin Elmer Turbochrome software.

20 Triglyceride Serum Levels in Mice Dosed with a Compound of the Invention is Compared to Mice Receiving the Vehicle to identify compounds which could be particularly useful for lowering triglycerides. Generally, triglyceride decreases of greater than or equal to 30% (thirty percent) compared to control following a 30 mg/kg dose suggests a compound that can be especially useful for lowering triglyceride levels.

25 The percent increase of HDLc serum levels in mice receiving a compound of the invention is compared to mice receiving vehicle to identify compounds of the invention that could be particularly useful for elevating HDL levels. Generally, and increase of greater than or equal to 25% (twenty five percent) increase in HDLc level following a 30 mg/kg dose suggests a compound that can be especially useful for elevating HDLc levels.

30 It may be particularly desirable to select compounds of this invention that both lower triglyceride levels and increase HDLc levels. However, compounds that either lower triglyceride levels or increase HDLc levels may be desirable as well.

Evaluation of Glucose Levels in db/db Mice

The effects upon plasma glucose associated with administering various dose levels of different compounds of the present invention and the PPAR gamma agonist
5 rosiglitazone (BRL49653) or the PPAR alpha agonist fenofibrate, and the control, to male db/db mice, are studied.

Five week old male diabetic (db/db) mice [for example, C57BlKs/j-m +/- Lepr(db), Jackson Laboratory, Bar Harbor, ME] or lean littermates are housed 6 per cage with food and water available at all times. After an acclimation period of 2 weeks,
10 animals are individually identified by ear notches, weighed, and bled via the tail vein for determination of initial glucose levels. Blood is collected (100 µl) from unfasted animals by wrapping each mouse in a towel, cutting the tip of the tail with a scalpel, and milking blood from the tail into a heparinized capillary tube. Sample is discharged into a heparinized microtainer with gel separator and retained on ice. Plasma is obtained after
15 centrifugation at 4°C and glucose measured immediately. Remaining plasma is frozen until the completion of the experiment, when glucose and triglycerides are assayed in all samples. Animals are grouped based on initial glucose levels and body weights. Beginning the following morning, mice are dosed daily by oral gavage for 7 days. Treatments are test compounds (30 mg/kg), a positive control agent (30 mg/kg) or vehicle
20 [1% carboxymethylcellulose (w/v)/ 0.25% Tween80 (w/v); 0.3 ml/mouse]. On day 7, mice are weighed and bled (tail vein) 3 hours after dosing. Twenty-four hours after the 7th dose (i.e., day 8), animals are bled again (tail vein). Samples obtained from conscious animals on days 0, 7 and 8 are assayed for glucose. After the 24-hour bleed, animals are weighed and dosed for the final time. Three hours after dosing on day 8, animals are
25 anesthetized by inhalation of isoflurane and blood obtained via cardiac puncture (0.5-0.7 ml). Whole blood is transferred to serum separator tubes, chilled on ice and permitted to clot. Serum is obtained after centrifugation at 4°C and frozen until analysis for compound levels. After sacrifice by cervical dislocation, the liver, heart and epididymal fat pads are excised and weighed.

30 Glucose is measured colorimetrically using commercially purchased reagents. According to the manufacturers, the procedures are modified from published work (McGowan, M. W., Artiss, J. D., Strandbergh, D. R. & Zak, B. Clin Chem, 20:470-5

(1974) and Keston, A. Specific colorimetric enzymatic analytical reagents for glucose. Abstract of papers 129th Meeting ACS, 31C (1956).); and depend on the release of a mole of hydrogen peroxide for each mole of analyte, coupled with a color reaction first described by Trinder (Trinder, P. Determination of glucose in blood using glucose
5 oxidase with an alternative oxygen acceptor. Ann Clin Biochem, 6:24 (1969)). The absorbance of the dye produced is linearly related to the analyte in the sample. The assays are further modified in our laboratory for use in a 96 well format. The commercially available standard for glucose, commercially available quality control plasma, and samples (2 or 5 µl/well) are measured in duplicate using 200 µl of reagent.
10 An additional aliquot of sample, pipetted to a third well and diluted in 200 µl water, provided a blank for each specimen. Plates are incubated at room temperature for 18 minutes for glucose on a plate shaker (DPC Micormix 5) and absorbance read at 500 nm on a plate reader. Sample absorbances are compared to a standard curve (100-800 for glucose). Values for the quality control sample are always within the expected range and
15 the coefficient of variation for samples is below 10%. All samples from an experiment are assayed at the same time to minimize inter-assay variability.

Evaluation of the Effects of Compounds of the Present Invention upon A^y Mice Body Weight, Fat Mass, Glucose and Insulin Levels

20

Female A^y Mice

Female A^y mice are singly housed, maintained under standardized conditions (22°C, 12 h light:dark cycle), and provided free access to food and water throughout the duration of the study. At twenty weeks of age the mice are randomly assigned to vehicle
25 control and treated groups based on body weight and body fat content as assessed by DEXA scanning (N=6). Mice are then dosed via oral gavage with either vehicle or a Compound of this invention (50 mg/kg) one hour after the initiation of the light cycle (for example, about 7 A.M.) for 18 days. Body weights are measured daily throughout the study. On day 14 mice are maintained in individual metabolic chambers for indirect
30 calorimetry assessment of energy expenditure and fuel utilization. On day 18 mice are again subjected to DEXA scanning for post treatment measurement of body composition.

The results of p.o. dosing of compound for 18 days on body weight, fat mass, and lean mass are evaluated and suggest which compounds of this invention can be especially useful for maintaining desirable weight and/or promoting desired lean to fat mass.

Indirect calorimetry measurements revealing a significant reduction in respiratory quotient (RQ) in treated animals during the dark cycle [0.864 ± 0.013 (Control) vs. 0.803 ± 0.007 (Treated); $p < 0.001$] is indicative of an increased utilization of fat during the animals' active (dark) cycle and can be used to select especially desired compounds of this invention. Additionally, treated animals displaying significantly higher rates of energy expenditure than control animals suggest such compounds of this invention can be especially desired.

Male KK/A^y Mice

Male KK/A^y mice are singly housed, maintained under standardized conditions (22°C, 12 h light:dark cycle), and provided free access to food and water throughout the duration of the study. At twenty-two weeks of age the mice are randomly assigned to vehicle control and treated groups based on plasma glucose levels. Mice are then dosed via oral gavage with either vehicle or a Compound of this invention (30 mg/kg) one hour after the initiation of the light cycle (7 A.M.) for 14 days. Plasma glucose, triglyceride, and insulin levels are assessed on day 14.

The results of p.o. dosing of compound for 14 days on plasma glucose, triglycerides, and insulin are evaluated to identify compounds of this invention which may be especially desired.

Method to Elucidate the LDL-cholesterol Total-cholesterol and Triglyceride Lowering Effect

Male Syrian hamsters (Harlan Sprague Dawley) weighing 80-120 g are placed on a high-fat cholesterol-rich diet for two to three weeks prior to use. Feed and water are provided ad libitum throughout the course of the experiment. Under these conditions, hamsters become hypercholesterolemic showing plasma cholesterol levels between 180-280 mg/dl. (Hamsters fed with normal chow have a total plasma cholesterol level between 100-150 mg/dl.) Hamsters with high plasma cholesterol (180 mg/dl and above) are

randomized into treatment groups based on their total cholesterol level using the GroupOptimizeV211.xls program.

5 A Compound of this invention is dissolved in an aqueous vehicle (containing CMC with Tween 80) such that each hamster received once a day approx. 1 ml of the solution by garvage at doses 3 and 30 mg/kg body weight. Fenofibrate (Sigma Chemical, prepared as a suspension in the same vehicle) is given as a known alpha-agonist control at a dose of 200 mg/kg, and the blank control is vehicle alone. Dosing is performed daily in the early morning for 14 days.

Quantification of Plasma Lipids:

10 On the last day of the test, hamsters are bled (400 µl) from the suborbital sinus while under isoflurane anesthesia 2 h after dosing. Blood samples are collected into heparinized microfuge tubes chilled in ice bath. Plasma samples are separated from the blood cells by brief centrifugation. Total cholesterol and triglycerides are determined by means of enzymatic assays carried out automatically in the Monarch equipment (Instrumentation
15 Laboratory) following the manufacturer's procedure. Plasma lipoproteins (VLDL, LDL and HDL) are resolved by injecting 25 µl of the pooled plasma samples into an FPLC system eluted with phosphate buffered saline at 0.5 ml/min through a Superose 6 HR 10/30 column (Pharmacia) maintained room temp. Detection and characterization of the isolated plasma lipids are accomplished by postcolumn incubation of the effluent with a
20 Cholesterol/HP reagent (for example, Roche Lab System; infused at 0.12 ml/min) in a knitted reaction coil maintained at 37°C. The intensity of the color formed is proportional to the cholesterol concentration and is measured photometrically at 505 nm.

The effect of administration of a Compound of this invention for 14 days is studied for the percent reduction in LDL level with reference to the vehicle group.
25 Especially desired compounds are markedly more potent than fenofibrate in LDL-lowering efficacy. Compounds of this invention that decrease LDL greater than or equal to 30% (thirty percent) compared to vehicle can be especially desired.

The total-cholesterol and triglyceride lowering effects of a Compound of this invention is also studied. The data for reduction in total cholesterol and triglyceride
30 levels after treatment with a compound of this invention for 14 days is compared to the vehicle to suggest compounds that can be particularly desired. The known control fenofibrate did not show significant efficacy under the same experimental conditions.

Method to Elucidate the Fibrinogen-Lowering Effect of PPAR α Modulators

Zucker Fatty Rat Model:

The life phase of the study on fibrinogen-lowering effect of compounds of this invention is part of the life phase procedures for the antidiabetic studies of the same compounds. On the last (14th) day of the treatment period, with the animals placed under surgical anesthesia, ~ 3ml of blood is collected, by cardiac puncture, into a syringe containing citrate buffer. The blood sample is chilled and centrifuged at 4°C to isolate the plasma that is stored at -70 °C prior to fibrinogen assay.

Quantification of Rat Plasma Fibrinogen:

Rat plasma fibrinogen levels are quantified by using a commercial assay system consists of a coagulation instrument following the manufacturer's protocol. In essence, 100 μ l of plasma is sampled from each specimen and a 1/20 dilution is prepared with buffer. The diluted plasma is incubated at 37°C for 240 seconds. Fifty microliters of clotting reagent thrombin solution (provided by the instrument's manufacturer in a standard concentration) is then added. The instrument monitors the clotting time, a function of fibrinogen concentration quantified with reference to standard samples. Compounds that lower fibrinogen level greater than vehicle can be especially desired. Cholesterol and triglyceride lowering effects of compounds of this invention are also studied in Zucker rats.

Method to Elucidate the Anti-body Weight Gain and Anti-appetite Effects of Compounds of this invention

Fourteen-Day Study in Zucker Fatty Rat¹ or ZDF Rat² Models :

Male Zucker Fatty rats, non-diabetic (Charles River Laboratories, Wilmington, MA) or male ZDF rats (Genetic Models, Inc, Indianapolis, IN) of comparable age and weight are acclimated for 1 week prior to treatment. Rats are on normal chow and water is provided ad libitum throughout the course of the experiment.

Compounds of this invention are dissolved in an aqueous vehicle such that each rat received once a day approximately 1 ml of the solution by gavage at doses 0.1, 0.3, 1 and 3 mg/kg body weight. Fenofibrate (Sigma Chemical, prepared as a suspension in the same vehicle) a known alpha-agonist given at doses of 300 mg/kg, as well as the vehicle are controls. Dosing is performed daily in the early morning for 14 days. Over the course of the experiment, body weight and food consumption are monitored. Using this assay, compounds of this invention are identified to determine which can be associated with a significant weight reduction.

10 Method to elucidate the activation of the PPAR delta receptor *in vivo*

This method is particularly useful for measuring the *in vivo* PPARdelta receptor activation of compounds of this invention that are determined to possess significant *in vitro* activity for that receptor isoform over the PPAR gamma isoform.

Male PPARa null mice (129s4 SvJae-PPARa^{tm1Gonz} mice; Jackson Laboratories) of 8-9 weeks of age are maintained on Purina 5001 chow with water ad libitum for at least one week prior to use. Feed and water are provided ad libitum throughout the course of the experiment. Using the GroupOptimizeV211.xls program, mice are randomized into treatment groups of five animals each based on their body weight.

20 Compounds of this invention are suspended in an aqueous vehicle of 1% (w/v) carboxymethylcellulose and 0.25% Tween 80 such that each mouse receives once a day approx. 0.2 ml of the solution by gavage at doses ranging from 0.2 to 20 mg/kg body weight. A control group of mice is included in each experiment whereby they are dosed in parallel with vehicle alone. Dosing is performed daily in the early morning for 7 days.

25 On the last day of dosing, mice are euthanized by CO₂ asphyxiation 3 hours after the final dose. Blood samples are collected by heart draw into EDTA-containing microfuge tubes and chilled on ice. Liver samples are collected by necropsy and are flash-frozen in liquid nitrogen and stored at -80 degrees Celsius. For RNA isolation from liver, five to ten mg of frozen liver is placed in 700 µl of 1x Nucleic Acid Lysis Solution (Applied Biosystems Inc., Foster City, CA) and homogenized using a hand-held tissue macerator (Biospec Products Inc., Bartlesville, OK). The homogenate is filtered through

an ABI Tissue pre-filter (Applied Biosystems Inc., Foster City, CA) and collected in a deep well plate on an ABI 6100 Nucleic Acid prep station (Applied Biosystems Inc., Foster City, CA). The filtered homogenate is then loaded onto an RNA isolation plate and the RNA Tissue-Filter-DNA method is run on the ABI 6100. The isolated RNA is
5 eluted in 150 µl of RNase free water. For quality assessment, 9 µl of the isolated RNA solution is loaded onto a 1% TBE agarose gel, and the RNA is visualized by ethidium bromide fluorescence.

Complementary DNA (cDNA) is synthesized using the ABI High Capacity Archive Kit (Applied Biosystems Inc., Foster City, CA). Briefly, a 2x reverse
10 transcriptase Master Mix is prepared according to the manufacturer's protocol for the appropriate number of samples (RT Buffer, dNTP, Random Primers, MultiScribe RT (50U/µl), RNase free water). For each reaction, 50 µl of 2x RT Master Mix is added to 50 µl of isolated RNA in a PCR tube that is incubated in a thermocycler (25°C for 10 minutes followed by 37°C for 2 hours). The resultant cDNA preparation is diluted 1:100
15 in dH₂O for analysis by real-time PCR. Also, a standard curve of cDNA is diluted 1:20, 1:100, 1:400, 1:2000, 1:10,000 for use in final quantitation.

A real-time PCR Master Mix for mouse Cyp4A1 gene expression is mixed to contain:

- 20 ▪ 1X Taqman Universal PCR Master Mix (Applied Biosystems Inc., Foster City, CA)
- 6 micromolar final concentration Forward primer; Qiagen/Operon Technologies, Alameda, CA)
- 6 micromolar final concentration Reverse primer (Qiagen/Operon Technologies, Alameda, CA)
- 25 ▪ 0.15 micromolar final concentration Probe (5' 6-FAM and 3' Tamra-Q; Qiagen/Operon Technologies, Alameda, CA)
- RNase free water to 10 microliters

A real-time PCR Master Mix for the 18S ribosomal RNA control gene expression is
30 mixed to contain

- 1X Taqman Universal PCR Master Mix (Applied Biosystems Inc., Foster City, CA)

- 0.34 micromolar Probe/Primer TaqMan® Ribosomal RNA Control Reagents #4308329 Applied Biosystems Inc., Foster City, CA)
- RNase free water to 10 microliters

5 For the real-time PCR analysis, 6 ul of the respective Master Mix solution (either Cyp4A1 or 18S) and 4 ul either of diluted cDNA or of Standard Curve samples is added to individual wells of a 384-well plate ($n = 2$ for Standards; $n = 4$ for unknowns). Reactions are performed using the ABI 7900 HT standard universal RT-PCR cycling protocol. Data are analyzed using SDS 2.1 (Applied Biosystems Inc., Foster City, CA).
10 Average quantity and standard deviation are calculated automatically for each individual sample, according to the standard curve values. Using Microsoft Excel 2000, mean values for each group of five individual mice is calculated. The mean value of each compound-treated group is divided by the mean value of the vehicle-treated group. The fold induction over the vehicle group is determined by assigning the vehicle group to the
15 value of 1.0, and the fold change of the mean value for each group is expressed as fold-induction versus vehicle (1.0). Data are plotted using Jandel SigmaPlot 8.0.

Monkey Studies

20 Efficacy Studies

Compounds of the invention may be examined in a dyslipidemic rhesus monkey model. After an oral dose-escalation study for 28 days in obese, non-diabetic rhesus monkeys a determination of HDL-c elevation is made with each dose and compared with pretreatment levels. LDL cholesterol is also determined with each dose. C-reactive
25 protein levels are measured and compared to pretreatment levels.

Compound of Formula 1 may be shown to elevate plasma HDL-cholesterol levels in an African Green Monkey model in a manner similar to that described above in rhesus monkeys.

Two groups of monkeys are placed in a dose-escalating study that consists of one
30 week of baseline measurements, 9 weeks of treatments (vehicle, Compound of Formula I), and four weeks of washout. During baseline, monkeys in all three groups are administered vehicle once daily for seven days. Test compound of Formula I, is

administered in vehicle once daily for three weeks, then at a greater concentration (double the dose may be desired) once daily for three weeks, and then a still greater concentration (double the most recent dose may be desired) once daily for three weeks. At the completion of treatment, monkeys in both groups are administered vehicle once daily and
5 monitored for an additional six weeks.

Animals are fasted overnight and then sedated for body weight measurements and blood collection at weeks 1 (vehicle), 2, 3, 4, 6, 7, 9, 10, 12, and 14 of the study.

Parameters to measured, for example:

- 10 Body weight
- Total plasma cholesterol
- HDL
- LDL
- Triglycerides
- 15 Insulin
- Glucose
- PK parameters at week 4, 7, and 10 (plasma drug concentration at last week of each dose)
- ApoAI
- 20 ApoAII
- ApoB
- ApoCIII
- Liver enzymes (SGPT, SGOT, α GT)
- Complete blood count
- 25 Additionally, other measures may be made, as appropriate, and consistent with the stated study design.

EQUIVALENTS

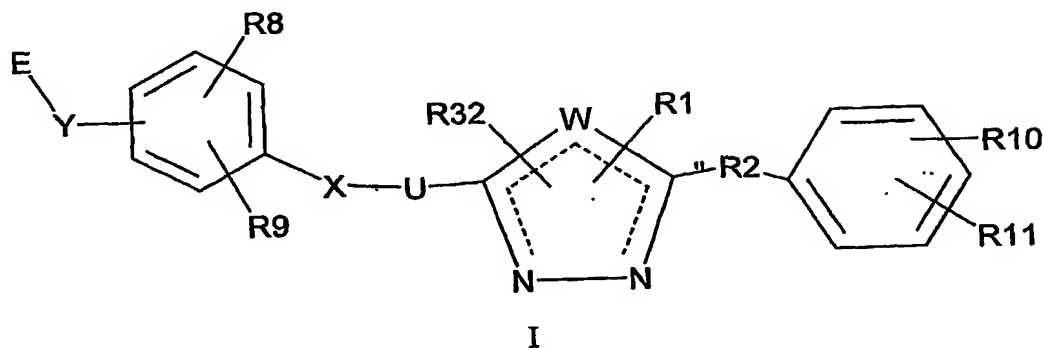
- 30 While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that

various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

- 5 1. A compound of the Formula I:



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

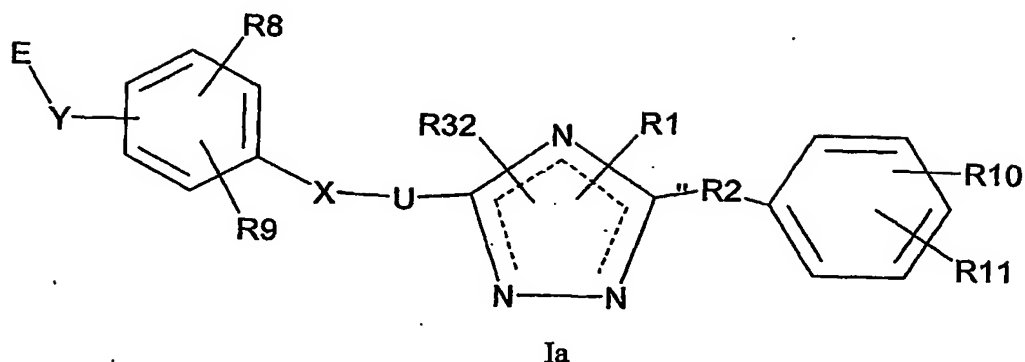
- 10 (a) R1 is selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ alkenyl, C₁-C₈ heteroalkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and, wherein C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents independently selected from R1';
- 15 (b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR₁₂, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₀₋₄-alkyl, heteroaryl, heterocycloalkyl, C(O)R₁₃, COOR₁₄, OC(O)R₁₅, OS(O)₂R₁₆, N(R₁₇)₂, NR₁₈C(O)R₁₉, NR₂₀SO₂R₂₁, SR₂₂, S(O)R₂₃, S(O)₂R₂₄, and S(O)₂N(R₂₅)₂; R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄ and R₂₅ are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- 20
- 25

- (c) R2 is selected from the group consisting of C₀-C₈ alkyl and C₁-4-heteroalkyl;
- (d) X is selected from the group consisting of a single bond, O, S, S(O)₂ and N;
- 5 (e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R30;
- (f) W is N, O or S;
- 10 (g) Y is selected from the group consisting of C, NH, and a single bond;
- (h) E is C(R3)(R4)A or A and wherein
- (i) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkylnitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R⁷;
- 15 (ii) each R⁷ is independently selected from the group consisting of hydrogen, C₁-C₆ haloalkyl, aryl C₀-C₄ alkyl and C₁-C₆ alkyl;
- (iii) R3 is selected from the group consisting of hydrogen, C₁-C₅ alkyl, and C₁-C₅ alkoxy; and
- 20 (iv) R4 is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R3 and R4 are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R26;
- 25 (i) R8 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, and halo;
- (j) R9 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, halo, aryl-C₀-C₄ alkyl, heteroaryl, C₁-C₆ allyl, and OR29, and wherein aryl-C₀-C₄ alkyl, heteroaryl are each optionally substituted with
- 30

from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C₁-C₄ alkyl;

- (k) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkylenyl, C₁-C₆ alkyl-COOR12'', C₀-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', OS(O)₂R16', N(R17')₂, NR18'C(O)R19', NR20'SO₂R21', SR22', S(O)R23', S(O)₂R24', and S(O)₂N(R25')₂; and wherein aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three independently selected from R28; and wherein R10 and R11 optionally combine to form a 5 to 6 membered fused bicyclic ring with the phenyl to which they are bound;
- (l) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (m) R30 is selected from the group consisting of C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and wherein C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents each independently selected from R31;
- (n) R32 is selected from the group consisting of a bond, hydrogen, halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, and C₁-C₆ alkyloxo; and
- "—" is optionally a bond to form a double bond at the indicated position.

2. A compound of the Formula Ia:



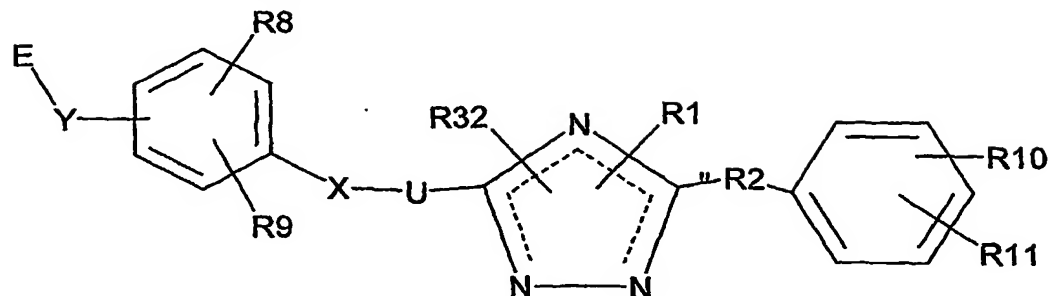
5 and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

- (a) R1 is selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and, wherein C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents independently selected from R1';
- (b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR₁₂, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₀₋₄-alkyl, heteroaryl, heterocycloalkyl, C(O)R₁₃, COOR₁₄, OC(O)R₁₅, OS(O)₂R₁₆, N(R₁₇)₂, NR₁₈C(O)R₁₉, NR₂₀SO₂R₂₁, SR₂₂, S(O)R₂₃, S(O)₂R₂₄, and S(O)₂N(R₂₅)₂; R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄ and R₂₅ are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (c) R2 is selected from the group consisting of C₀-C₈ alkyl and C₁₋₄-heteroalkyl;
- (d) X is selected from the group consisting of a single bond, O, S, S(O)₂ and N;

- (e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R30;
- 5 (f) Y is selected from the group consisting of C, NH, and a single bond;
- (g) E is C(R3)(R4)A or A and wherein
- (i) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkyl nitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from
- 10 R⁷;
- (ii) each R⁷ is independently selected from the group consisting of hydrogen, C₁-C₆ haloalkyl, aryl C₀-C₄ alkyl and C₁-C₆ alkyl;
- (iii) R3 is selected from the group consisting of hydrogen, C₁-C₅ alkyl, and C₁-C₅ alkoxy; and
- 15 (iv) R4 is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R3 and R4 are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R26;
- 20 (h) R8 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, and halo;
- (i) R9 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, halo, aryl-C₀-C₄ alkyl, heteroaryl, C₁-C₆ allyl, and OR29, and wherein aryl-C₀-C₄ alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C₁-C₄ alkyl;
- 25 (j) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkylenyl, C₁-C₆ alkyl-COOR12'', C₀-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆
- 30

- haloalkyloxy, C₃-C₇ cycloalkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, aryloxy, C(O)R_{13'}, COOR_{14'}, OC(O)R_{15'}, OS(O)₂R_{16'}, N(R_{17'})₂, NR_{18'}C(O)R_{19'}, NR_{20'}SO₂R_{21'}, SR_{22'}, S(O)R_{23'}, S(O)₂R_{24'}, and S(O)₂N(R_{25'})₂; and wherein aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three independently selected from R₂₈; and wherein R₁₀ and R₁₁ optionally combine to form a 5 to 6 membered fused bicyclic ring with the phenyl to which they are bound;
- 10 (k) R_{12'}, R_{12''}, R_{13'}, R_{14'}, R_{15'}, R_{16'}, R_{17'}, R_{18'}, R_{19'}, R_{20'}, R_{21'}, R_{22'}, R_{23'}, R_{24'}, and R_{25'} are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (l) R₃₀ is selected from the group consisting of C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and wherein C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents each independently selected from R₃₁;
- 15 (m) R₃₂ is selected from the group consisting of a bond, hydrogen, halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, and C₁-C₆ alkyloxy; and
- 20 (n) ---- is optionally a bond to form a double bond at the indicated position.

3. A compound of the Formula Ia:



Ia

and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates

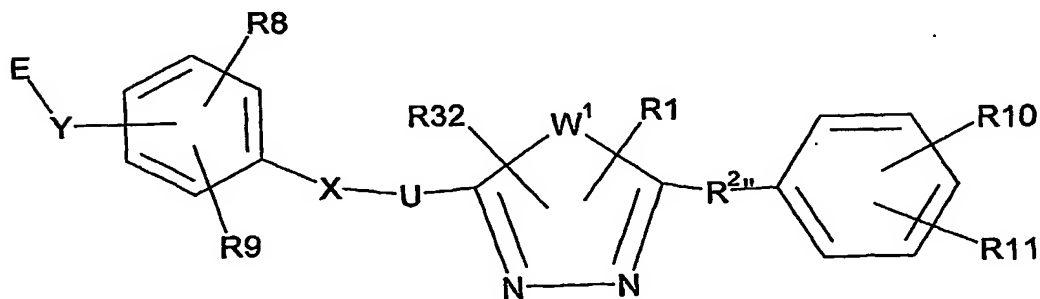
5 thereof, wherein:

- (a) R1 is selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ alkenyl, C₁-C₈ heteroalkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and, wherein C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents independently selected from R1';
- (b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR₁₂, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₀₋₄-alkyl, heteroaryl, heterocycloalkyl, C(O)R₁₃, COOR₁₄, OC(O)R₁₅, OS(O)₂R₁₆, N(R₁₇)₂, NR₁₈C(O)R₁₉, NR₂₀SO₂R₂₁, SR₂₂, S(O)R₂₃, S(O)₂R₂₄, and S(O)₂N(R₂₅)₂; R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄ and R₂₅ are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (c) R2 is selected from the group consisting of C₀-C₈ alkyl and C₁₋₄-heteroalkyl;
- (d) X is selected from the group consisting of a single bond, O, S, S(O)₂ and N;

- (e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is substituted with from one to four substituents each independently selected from R30;
- 5 (f) Y is selected from the group consisting of C, O, S, NH and a single bond;
- (g) E is C(R3)(R4)A or A and wherein
- (i) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkyl nitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R⁷;
- 10 (ii) each R⁷ is independently selected from the group consisting of hydrogen, C₁-C₆ haloalkyl, aryl C₀-C₄ alkyl and C₁-C₆ alkyl;
- (iii) R3 is selected from the group consisting of hydrogen, C₁-C₅ alkyl, and C₁-C₅ alkoxy; and
- 15 (iv) R4 is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R3 and R4 are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R26;
- 20 (h) R8 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, and halo;
- (i) R9 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, halo, aryl-C₀-C₄ alkyl, heteroaryl, C₁-C₆ allyl, and OR29, and wherein aryl-C₀-C₄ alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C₁-C₄ alkyl;
- 25 (j) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkylenyl, C₁-C₆ alkyl-COOR12'', C₀-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆
- 30

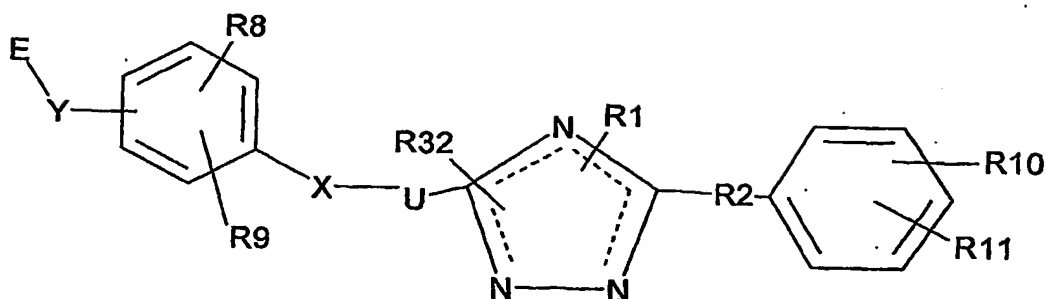
- haloalkyloxy, C₃-C₇ cycloalkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, aryloxy, C(O)R₁₃', COOR₁₄', OC(O)R₁₅', OS(O)₂R₁₆', N(R₁₇')₂, NR₁₈'C(O)R₁₉', NR₂₀'SO₂R₂₁', SR₂₂', S(O)R₂₃', S(O)₂R₂₄', and S(O)₂N(R₂₅')₂; and wherein aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three independently selected from R₂₈; and wherein R₁₀ and R₁₁ optionally combine to form a 5 to 6 membered fused bicyclic ring with the phenyl to which they are bound;
- (k) R₁₂', R₁₂'', R₁₃', R₁₄', R₁₅', R₁₆', R₁₇', R₁₈', R₁₉', R₂₀', R₂₁', R₂₂', R₂₃', R₂₄', and R₂₅' are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (l) R₃₀ is selected from the group consisting of C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and wherein C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents each independently selected from R₃₁;
- (m) R₃₂ is selected from the group consisting of a bond, hydrogen, halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, and C₁-C₆ alkyloxy; and
- (n) — is optionally a bond to form a double bond at the indicated position.

4. A compound of the Formula Ib:



25 wherein W₁ is S or O.

5. A compound of the Formula III:



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates

5 thereof, wherein:

- (a) R1 is selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ alkenyl, C₁-C₈ heteroalkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and, wherein C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents independently selected from R1';
- (b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR₁₂, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₀₋₄-alkyl, heteroaryl, heterocycloalkyl, C(O)R₁₃, COOR₁₄, OC(O)R₁₅, OS(O)₂R₁₆, N(R₁₇)₂, NR₁₈C(O)R₁₉, NR₂₀SO₂R₂₁, SR₂₂, S(O)R₂₃, S(O)₂R₂₄, and S(O)₂N(R₂₅)₂; R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄ and R₂₅ are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (c) R2 is selected from the group consisting of C₀-C₈ alkyl and C₁₋₄-heteroalkyl;
- (d) X is selected from the group consisting of a single bond, O, S, S(O)₂ and N;

- (e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R30;
- 5 (f) Y is selected from the group consisting of O, S, NH, C, and a single bond;
- (g) E is C(R3)(R4)A; wherein
- (i) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkynitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R⁷;
- 10 (ii) each R⁷ is independently selected from the group consisting of hydrogen, C₁-C₆ haloalkyl, aryl C₀-C₄ alkyl and C₁-C₆ alkyl;
- (iii) R3 is selected from the group consisting of C₁-C₅ alkyl, and C₁-C₅ alkoxy; and
- 15 (iv) R4 is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R3 and R4 are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R26;
- 20 with the proviso that when Y is O then R4 is selected from the group consisting of C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R3 and R4 are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, cycloalkyl and aryl-alkyl are each optionally substituted with one to three each independently selected from R26;
- 25 (h) R8 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, and halo;
- 30 (i) R9 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, halo, aryl-C₀-C₄ alkyl, heteroaryl, C₁-C₆ allyl, and OR29, and

wherein aryl-C₀-C₄ alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C₁-C₄ alkyl;

- 5 (j) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkylenyl, C₁-C₆ alkyl-COOR12'', C₀-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryl-C₀-4-alkyl, aryl- C₁-4-heteroalkyl, heteroaryl-C₀-4-alkyl, C3-C6 cycloalkylaryl-C₀-2-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', OS(O)₂R16', N(R17')₂, NR18'C(O)R19', NR20'SO₂R21', SR22', S(O)R23', S(O)₂R24', and S(O)₂N(R25')₂; and wherein aryl-C₀-4-alkyl, aryl- C₁-4-heteroalkyl, heteroaryl-C₀-4-alkyl, and C3-C6 cycloalkylaryl-C₀-2-alkyl are each optionally substituted with from one to three independently selected from R28; and wherein R10 and R11 optionally combine to form a 5 to 6
10 15 membered fused bicyclic ring with the phenyl to which they are bound;
- (k) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (l) R30 is selected from the group consisting of C₁-C₆ alkyl, aryl-C₀-4-alkyl, aryl- C₁-4-heteroalkyl, heteroaryl-C₀-4-alkyl, and C3-C6 cycloalkylaryl-C₀-2-alkyl, and wherein C₁-C₆ alkyl, aryl-C₀-4-alkyl, aryl- C₁-4-heteroalkyl, heteroaryl-C₀-4-alkyl, and C3-C6 cycloalkylaryl-C₀-2-alkyl are each optionally substituted with from one to three substituents each independently selected from R31;
- 20 (m) R32 is selected from the group consisting of a bond, hydrogen, halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, and C₁-C₆ alkyl-oxo; and
- 25 (n) --- is optionally a bond to form a double bond at the indicated position.

6. A compound as claimed by any one of Claims 1 through 3 wherein X is - O-.
7. A compound as claimed by any one of Claims 1 through 3 wherein X is - S-.
8. A compound as claimed by any one of Claims 2 through 5 wherein Y is O.
9. A compound as claimed by any one of Claims 2 through 5 wherein Y is C.
10. A compound as claimed by any one of Claims 1 through 5 wherein Y is S.
11. A compound as claimed by any one of Claims 1 through 8 wherein ---- is a bond to form a double bond at the designated location on Formula I.
12. A compound as claimed by any one of Claims 1 through 8 wherein two of "----" in the five membered ring are each a bond to form double bonds at the designated locations.
13. A compound as claimed by any one of Claims 1 through 10 wherein E is C(R3)(R4)A.
14. A compound as claimed by any one of Claims 1 through 11 wherein A is COOH.
15. A compound as claimed by any one of Claims 1 through 12 wherein R10 is haloalkyl.
16. A compound as claimed by any one of Claims 1 through 12 wherein R10 is CF₃.

17. A compound as claimed by any one of Claims 1 through 12 wherein R10 is haloalkyloxy.

18. A compound as claimed by any one of Claims 1 through 12 wherein R10 and R11 are each independently selected from the group consisting of hydrogen, halo, 5 oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR₁₂'', C₁-C₆ alkoxy, C₁-C₆ haloalkyl, and C₁-C₆ haloalkyloxy.

19. A compound as claimed by any one of Claims 1 through 12 wherein R10 is selected from the group consisting of C₃-C₇ cycloalkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄- 10 heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and aryloxy.

20. A compound as claimed by any one of Claims 1 through 17 wherein R1 is optionally substituted C₂-C₃ arylalkyl.

21. A compound as claimed by any one of Claims 1 through 17, wherein R8 and R9 are each independently selected from the group consisting of hydrogen and C₁-C₃ 15 alkyl.

22. A compound as claimed by any one of Claims 1 through 17 and 19 20 wherein R1, R2, R3, and R4 are each independently selected from the group consisting of C₁-C₂ alkyl.

23. A compound as claimed by any one of Claims 1 through Claim 17 and 19 wherein R1, R3, and R4 are each independently selected from the group consisting of 25 hydrogen and C₁-C₂ alkyl.

24. A compound as claimed by any one of Claims 1 through 17 wherein R2 is a bond.

25. A compound as claimed by any one of Claims 1 through 19 wherein R2 is selected from the group consisting of C₀-C₁ alkyl. 30

26. A compound as claimed by any one of Claims 1 through 23 wherein U is C₁-C₃ alkyl.

27. A compound as claimed by any one of Claims 1 through 24 wherein U is saturated.

28. A compound as claimed by any one of Claims 1 through 25 wherein U is substituted with C₁-C₃ alkyl.

29. A compound as claimed by any one of Claims 24, 25 and 26 wherein one carbon of the aliphatic linker is replaced with an O.

30. A compound as claimed by any one of Claims 24, 25 and 26 wherein U is an aliphatic linker having one carbon replaced by N.

31. A compound as claimed by any one of Claims 1 through 26 wherein U is an aliphatic linker having one carbon replaced by S.

32. A compound as claimed by any one of Claims 1 through 28 wherein the aliphatic linker is substituted with from one to three substituents each independently selected from R30.

33. A compound as claimed by Claim 29 wherein the aliphatic linker is substituted with from one to two substituents each independently selected from R30.

34. A compound as claimed by any one of Claims 1 through 31 wherein each R30 is independently selected from the group consisting of C₁-C₆ alkyl.

35. A compound as claimed by any one of Claims 1 through 32 wherein each R30 is independently selected from the group consisting of C₂-C₃ alkyl.

36. A compound as claimed by any one of Claims 1 through 31 wherein R30 is independently selected from the group consisting of aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C3-C6 cycloalkylaryl-C₀₋₂-alkyl.

5 37. A compound as claimed by any one of Claims 1 through 34 wherein two of "—" each form a double bond in the five membered ring at the designated position.

38. A compound as claimed by Claim 35 wherein Y is O and E is -CH₂COOH.

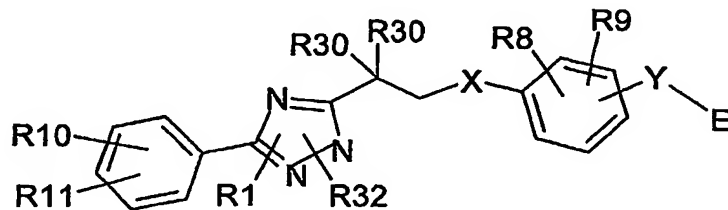
10

39. A compound as claimed by any one of Claims 1 through 38 wherein U is substituted with methyl.

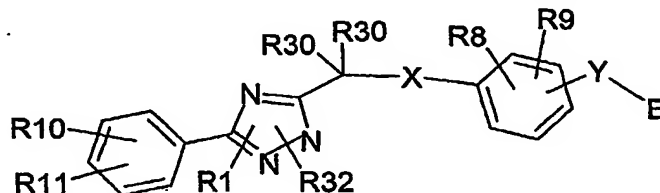
40. A compound as claimed by any one of Claims 1 through 38 or one of
15 Claims 32 through 39 wherein U is methylene.

41. A compound as claimed by any one of Claims 1 through 12, Claims 18 through 40 wherein R10 and R11 combine to form a fused 6 membered ring.

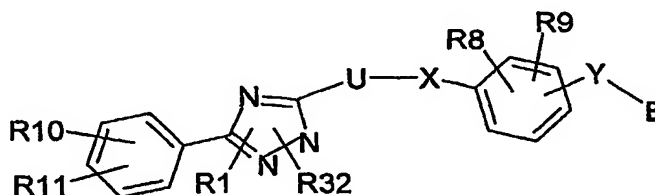
20 42. A compound as claimed by any one of Claims 1 through 10, one of Claims 17 through 25, or one of Claims 27 through 37 represented by the following Structural Forumula IV:



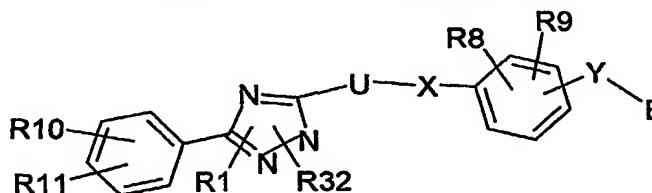
43. A compound as claimed by any one of Claims 1 through 10, or one of Claims 17 through 38 represented by the following Structural Formula V:



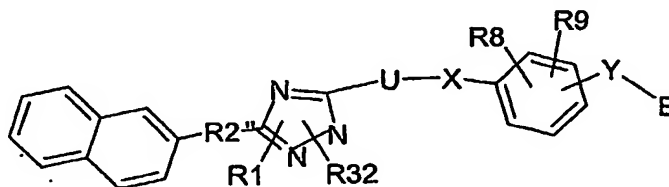
5 44. A compound as claimed by any one of Claims Claims 1 through 10, or one of Claims 17 through 40 represented by the following Structural Formula VI:



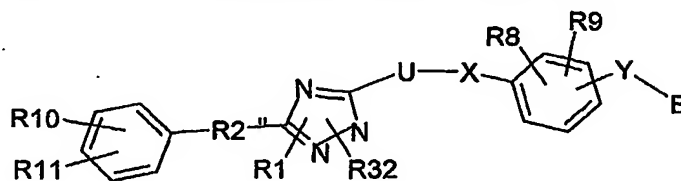
45. A compound as claimed by any one of Claims 1 through 10 or one of
10 Claims 17 through 40 represented by the following Structural Formula VII:



46. A compound as claimed by any one of Claims 1 through 10, Claims 17
through 40 represented by the following Structural Formula VIII:



47. A compound as claimed by any one of Claims 1 through 10, Claims 17 through 40 represented by the following Structural Formula IX:

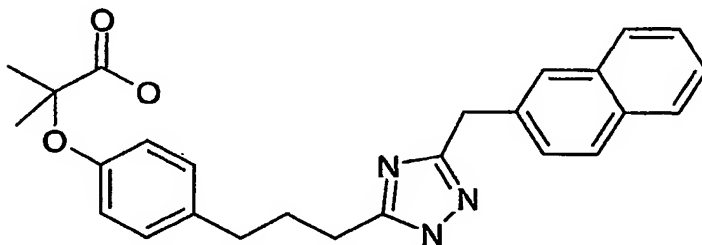


5 48. A compound as claimed by any one of Claims 1 through 47 wherein X and Y are substituted at a 1,4-position, such that X and Y are para substituted to one another.

49. A compound as claimed by any of of Claims 1 through 47 wherein X and Y are substituted at a 1,3-position, such that X and Y are meta substituted to one another.

10

50. A compound as claimed by any one of Claims 1 through 3 wherein the compound is a compound of the formula:



or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

15 51. A compound as claimed by any one of Claims 1 through 49 wherein X is a bond.

52. A compound as claimed by any one of Claims 1 through 3 which is 2-Methyl-2-{4-[3-(5-naphthalen-2-ylmethyl-2H-[1,2,4]triazol-3-yl)-phenoxy}propionic acid.

20

53. A compound as claimed by any one of Claims 1 through 52 that is the S conformation.

54. A compound as claimed by any one of Claims 1 through 52 that is the R conformation.

55. A pharmaceutical composition, comprising as an active ingredient, at least one compound as claimed by any one of Claims 1 through 54 together with a pharmaceutically acceptable carrier or diluent.

56. A method of modulating a peroxisome proliferator activated receptor, comprising the step of contacting the receptor with at least one compound as claimed by any one of Claims 1 through 54.

57. A method of treating diabetes mellitus in a mammal, comprising the step of administering to the mammal in need thereof a therapeutically effective amount of at least one compound of Claims 1 through 54.

58. A method of treating metabolic disorder in a mammal, comprising the step of administering to the mammal in need thereof a therapeutically effective amount of at least one compound of Claims 1 through 54.

59. A method of Claim 58 wherein the mammal in need thereof is diagnosed as suffering from metabolic disorder.

60. A method of selectively modulating a PPAR delta receptor comprising administering a compound as claimed by any one of Claims 1 through 54 to a mammal in need thereof.

61. The manufacture of a medicament for use in the treatment and/or prevention of a condition mediated by nuclear receptors, in particular by a peroxisome proliferator activated receptor, wherein the compound is a compound as claimed by any one of Claims 1 through 54.

62. A method of treating atherosclerosis in a mammal, comprising the step of administering to the mammal in need thereof, a therapeutically effective amount of at least one compound of Claims 1 through 54.

5 63. A compound as Claimed by any one of Claims 1 through 54 for use as a pharmaceutical.

64. A method for treating or preventing the progression of cardiovascular disease in a mammal in need thereof comprising administering a therapeutically effective
10 amount of a compound as Claimed by any one of Claims 1 through 54.

65. A method as claimed by Claim 64 wherein the mammal is diagnosed as being in need of such treatment.

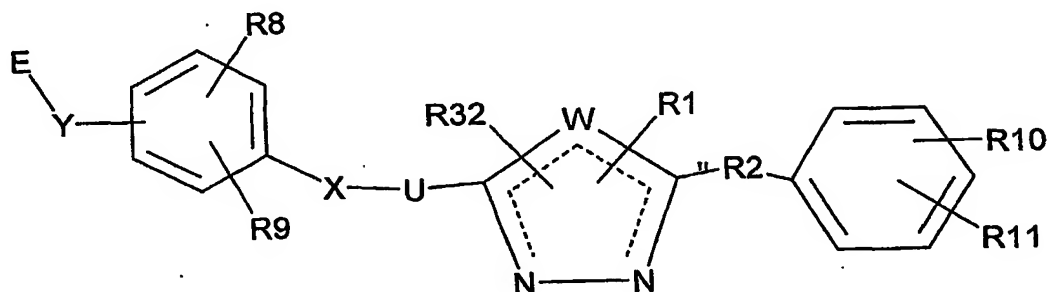
15 66. A compound as claimed by any one of Claims 1 through 54 wherein the compound is radiolabeled.

67. A compound as disclosed by any one of the Examples herein.

20 68. All methods disclosed herein of preparing the compounds represented by Structural Formula I.

ABSTRACT

The present invention is directed to compounds represented by the following structural formula, Formula I:



wherein:

- 10
- (a) X is selected from the group consisting of a single bond, O, S, S(O)₂ and N;
 - (b) U is an aliphatic linker;
 - (c) Y is selected from the group consisting of O, C, S, NH and a single bond;
 - (d) W is N, O or S;
 - 15 (e) E is C(R₃)(R₄)A or A and wherein;
 - (f) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkynitrile, carboxamide, sulfonamide and acylsulfonamide.

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

☒ **BLACK BORDERS**

☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**

☒ **FADED TEXT OR DRAWING**

☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**

☐ **SKEWED/SLANTED IMAGES**

☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**

☐ **GRAY SCALE DOCUMENTS**

☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**

☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**

☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.